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SOME NEW DRUGS AND REMEDIES*

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If even half the statements were true which have been made concerning new drugs by their inventors and manufacturers during the last decade or so then it would scarcely be too much to say that by now all the problems of medicine would have been solved. Not only would there be no need for any further research, but the practice of medicine would have been reduced to such simplicity that, beyond a knowledge of diagnosis, all we should now require would be a fountain-pen and the ability to construct and use a card index. It is a curious phenomenon, yet one which has been attested again and again by medical history, that at the commencement of its career a new drug often meets with a striking success; all too often, however, after a time, the drug in question is found to be useless, harmful, or at best of but limited application. It was Trousseau who once said to his students, "Make haste, gentlemen, to use a new drug while it still has power to cure!"

This is not to say, of course, that there have been no real advances in drug therapy during, say, the last twenty-five years. To mention no other instances, the discovery of insulin, of liver and stomach preparations in the treatment of pernicious and some other anaemias, and the promising developments of serum, vaccine, and glandular therapy would dispel any undue pessimism. Then, too, many new synthetic drugs of proved usefulness have been added during that period to our armamentarium by the research and ingenuity of chemical and other workers. Yet, considering the spate of new drugs which has in ever-increasing volume poured forth from the laboratories of the world, the number proved to be of real and permanent value has not been nearly so large as might reasonably have been expected.

I propose to deal with just a few groups of remedies which present problems of practical importance to the practitioner in his daily work. More especially I shall deal with those classes of substances about which there is still some controversy, and I shall try to tell you what is at present being thought about them. Therefore I shall have but little to say about proved and universally accepted new remedies; not because they are undeserving of lengthy consideration, but simply because good wine needs no bush. I shall include certain drugs and remedies which, though known for long, have recently been presented to us under new names, with new claims, by certain proprietary houses. And this brings me to my first group, which I shall term:

Pseudo-new Remedies

Among pseudo-new remedies may be mentioned the class in which a well-known pharmacopoeial drug—for example, acetylsalicylic acid—is rebaptized and offered to the profession, often also to the public, at an increased price as a new drug of surpassing excellence. A drug by any other name than the official one is for some mysterious reason thought to act twice as well. To make it twice, or thrice, as expensive is good psychology, because most of us associate together the adjectives "cheap" and "nasty," and are prone to conclude that what is dear must necessarily be good. There is, too, as a general rule, a claim to unheard-of purity or safety. As regards the claim of purity, to take a concrete case—namely, that of aspirin—the *Pharmacopoeia* enjoins a purity of not less than 99.5 per cent., so that there is only the half per cent. for the manufacturer to play with. Even if he has managed to narrow this to a still smaller fraction is it worth while to pay three or four times as much for a degree of purity considered unnecessary by the *Pharmacopoeia*? If, on the other hand, the manufacturer advertises that his is the "safe" brand of so-and-so he creates in our impressionable and conscientious minds the fear that we may be guilty of manslaughter if we order the pharmacopoeial article. "Safe" in this connexion might mean one of two things. It might mean that a drug whose therapeutic properties are dependent upon its dangerous character has been rendered innocuous. If so, then the manufacturer has only succeeded in emasculating it. But if what is meant is that the pharmacopoeial article is dangerous, then an unjust aspersion is being cast upon the very worthy compilers of the 1932 *Pharmacopoeia*, who, I can assure you, had no ancestors among the Borgias.

Another group of drugs, the glycerophosphates, has been known for some time, but as many elegant preparations of them are still being put on the market they may, I think, rightly be included in this group of pseudo-new remedies. The best pharmacologists have long been in agreement that, in so far as the utilization of phosphorus is concerned, these drugs are quite inert and have no therapeutic usefulness. They are rapidly broken up in the body and excreted as inorganic salts, while the glycerin undergoes combustion. They may have a certain value in respect of the iron, calcium, strychnine, or other drug which is combined with the glycerophosphoric acid, but this is a very extravagant and uneconomical way of prescribing iron, calcium, etc. In the light of modern knowledge the prescription of glycerophosphates is now seen to be irrational and unscientific.

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The hypophosphites constitute a still older group of remedies. As in the case of the glycerophosphates, there is no justification for giving hypophosphites for their phosphorus content, since they are almost entirely eliminated and little or no assimilation of the phosphorus occurs. It has been calculated that half a glass of milk contains more available phosphorus than 45 grains of the hypophosphites. They have been deleted from the 1932 edition of the *British Pharmacopoeia*.

Lastly among pseudo-new remedies we may mention those elegant and expensive preparations in which well-known drugs are combined, put up under a registered name, and claimed to be more efficacious than any substitute, even though made with the same ingredients. There is no doubt about their artistic appearance, but unfortunately the Philistine Insurance Act takes no account of Art; its criterion is whether a drug or remedy can be regarded as reasonably necessary for adequate treatment. Moreover, many of the best of these formulae are contained in the *British Pharmaceutical Codex*, and can be made up by the chemist round the corner at quite a reasonable price.

Erstwhile Proprietary Preparations

There are certain valuable modern drugs which, starting their career as proprietary articles, are now available under both trade names and their ordinary chemical designations. Considering more especially drugs of a definite chemical composition, as, for example, phenobarbitone and phenobarbitone sodium, which are now included in the *British Pharmacopoeia*, it is reasonable to suppose that drugs ordered under these names should be quite as efficacious as when ordered under their original proprietary names. Yet because the former are much cheaper than the latter some hesitate to write the pharmacopoeial names. On this point reference might be made to a paper by Dr. Handley in the *Journal of Mental Science* for July, 1934. He tested a proprietary brand against the non-proprietary official soluble phenobarbitone. To a series of 200 epileptic patients he gave the proprietary brand, and to a control series of 200 like patients he gave the pharmacopoeial equivalent. The doses were the same in each series, and he continued the experiment for four months. In no case did he find that the non-proprietary brand produced results less satisfactory than the proprietary article. The economical gain was, however, considerable, representing as it did a difference of some seven shillings an ounce in favour of the non-proprietary drug.

Colloidal Preparations

In view of the claims made by interested parties many practitioners must have wondered whether the presentation of drugs in the form of colloidal solutions endows them with mysterious properties which are not present when they are given as ordinary solutions. The answer is No, though in some cases, not perhaps very many, there are certain advantages. The subject is rather a difficult one, and the exact evaluation of the colloidal preparations from a therapeutic standpoint is not easy for a variety of reasons. The chief difficulty lies in the fact that, in order to render these preparations stable, various "protectives" of an organic nature have to be added, such as gelatin, glutamine, glucose, peptone, etc. These protective substances often have a definite action of their own, especially when injected, and in some of the market preparations the active ingredient would appear to be not in colloidal solution at all, but in chemical combination with a body of colloid nature. Another difficulty is that very little is at present known of the fate of colloidal

solutions in the body, but it seems probable that, if given by the mouth, they are altered by the digestive fluids, and so any supposed advantage will be lost. If injected, we have to discount the effect of the protective colloid, which, being commonly of a protein nature, may exert an action similar to that of the substances used in non-specific protein therapy. Nor must we forget that, as the late Sir William Bayliss pointed out, various membranes of the body are impermeable by substances in the colloid state although large particles can be taken up by many cells. It is quite incorrect to say, as has been said, that drugs must be colloidal before they can exert their effects.

Besides all this, it has been shown that some of the preparations on the market cannot be regarded as true colloids, and that in others the active principle is present in such minute quantity that it is inconceivable that it can exert any appreciable effect. A well-known colloidal preparation of calcium, for example, was examined by the Council on Pharmacy and Chemistry of the American Medical Association and, in the dose recommended by the makers, was found to contain about as much calcium as that in a quarter to half a teaspoonful of milk! Moreover, owing to the nature of the substance with which the calcium was combined, there was considerable doubt whether even this minute quantity of the metal would be as well absorbed as when given in the form of milk. Let me say here that for reliable information on many well-advertised new drugs and remedies you will find *New and Non-Official Remedies*, published in Chicago by the American Medical Association, an exceedingly useful book.

It would appear that, generally speaking, the idea must be abandoned that drugs administered in the colloidal state have a more powerful action than when given in ordinary solution. With perhaps one or two exceptions the reverse is the case, and any therapeutic advantage of colloids must be attributed to the fact that they have a slow, gradual effect. This is brought about, to quote Bayliss again, by "the very slow and prolonged action of continuous minute doses of the ionized form" into which the colloidal form changes. If, therefore, this particular action is required, the injection or local application of a true colloidal solution may be of value as forming a reservoir of the drug for slow and continuous utilization. This would explain the undoubted usefulness in certain circumstances of the colloidal silver preparations. Colloidal kaolin, again, is stated to have stronger absorptive properties in the colloidal state than in the form of gross particles, owing to the larger total surface area of the colloidal particles.

To sum up the matter: I think it would be fair to say, in the light of our present knowledge, that while there are no mysterious properties in colloidal drugs, and while their field of usefulness is strictly limited, circumstances do sometimes occur in which they have an advantage over drugs in the ordinary forms. For oral administration, however, they have no advantages over ordinary solutions, and there is the very real disadvantage of greatly increased cost.

Valueless Endocrine Preparations

The endocrine preparations which have been and are being offered to the physician may conveniently be divided into three classes:

1. Those concerning which there is no reliable evidence of usefulness;
2. Those whose efficacy has been proved "beyond a peradventure";
3. Those concerning which opinion is at present in a fluid state.

As regards the first class, tablets and solutions have been prepared from almost every tissue and organ of the animal body, regardless of whether those tissues and organs could reasonably be supposed to produce an internal secretion or not. Thus we have extracts of tonsil, kidney, prostate, spleen, heart, brain, mammary gland, and so on. I know of no authentic evidence that such products are of the slightest use, with the exceptions that certain brain extracts seem to have some haemostatic effect, and a German author claims to have isolated a "heart hormone," which is being tried out in cases of angina pectoris. Doubtless, from time to time, either by the chance co-operation of the *vis medicatrix naturae* or through the influence of suggestion, apparent successes have been reported. It is surprising what brilliant results can follow when a new drug or preparation is swallowed, along with its advertisement. Yet, in so far as real scientific evidence is concerned, there is at present none, and such therapy rests on no sounder theory than that of the savage who eats his enemy's heart to absorb his courage. Equally unscientific are those "shotgun" preparations of various combinations of endocrines which are so largely advertised, especially as nearly all of them are intended for oral administration. That they have any action at all is due to the fact that one of the ingredients of the cartridge is usually thyroid extract, which is one of the very few preparations of endocrine nature having any action when given by the mouth. These polyglandular preparations are also irrational when considered from another point of view. It would appear that true polyglandular syndromes are excessively rare, and Rowe (quoted by Cameron) states that in a series of over 5,000 cases he "has seen but two or three in which there has been apparently a coexistent primary disturbance in more than one endocrine gland."

Also in this class come those pancreatic and guanidine-like preparations which have been and still are advertised as being efficacious in diabetes when given by the mouth. Such a statement ought not to be made at this time of day, for again and again careful tests with controls have been made which show that it is quite useless to prescribe such products. We all wish we could relieve our diabetics from the inconvenience of the needle-prick, but at present there is no other effective method of treatment.

Endocrine Preparations of Proved Worth

This group includes the thyroid, parathyroid, posterior pituitary, and suprarenal gland preparations, and insulin, and we ought, perhaps, to include the liver and stomach preparations. Except in the case of the thyroid, liver, and stomach preparations there is little or no evidence that any definite systemic effect is produced by oral administration, though there is reason to believe that the nasal mucous membrane is able to absorb a certain amount of the posterior pituitary principle in snuff or in solution. I ought also to mention, in passing, the recent and extremely interesting researches on the action of extracts derived from the cortex of the suprarenal glands in Addison's disease. Adrenaline, of course, is derived from the medulla of the gland. A certain amount of success has already been attained, and in the case of these cortical extracts there is definite proof that they are effective by the mouth as well as by injection, though the latter method is the more powerful.

The third group, of endocrine preparations about which opinion is still uncertain, we must consider in more detail because, in respect of some of its members, and especially the sex hormones, practical everyday problems arise, and a brief statement of the present position of our knowledge may be of advantage.

Endocrine Preparations of Indefinite Value

We may dismiss at once the testicular extracts and preparations as being at present of no definite therapeutic importance. A good deal of work is being done upon them, but much more is required before a therapeutic rationale can be worked out. We must wait and see whether they prove to be of any real value in human treatment. But after a long period of confusion and conflicting opinion, which is even yet not quite resolved, some light is at last being thrown upon the possibilities of the ovarian principles and those of the corpus luteum.

Recent work on the endocrine machinery of the menstrual cycle has shown that three groups of hormones are involved. These are the so-called gonadotropic principles of the anterior pituitary (prolan A and prolan B), the follicular ovarian hormones, and the hormone of the corpus luteum. Prolan A stimulates follicle formation, while prolan B stimulates the formation of the corpus luteum hormone. Now as regards the ovarian follicular and the corpus luteum hormones, each has an important part to play at definite periods of the menstrual cycle. The follicular hormone, in the first half of the menstrual cycle, causes proliferation of the endometrium, while the transformation into the secretion phase in the second half is caused by the hormone manufactured by the yellow substance of the corpus luteum. Both are essential, and thus we can already deduce from this recent work that it is useless to attempt to treat amenorrhoea, as was so often attempted in the past, merely by giving the ovarian follicular principle alone.

Another important result of recent work has been to show that the older forms of ovarian substance, ovarian residue and corpus luteum, were inert, or almost inert, and what little active principle they did contain was rendered useless, or nearly useless, by the digestive juices. Up to quite recently the endocrine treatment of ovarian disorders was blind, groping, and almost wholly ineffective owing mainly to two things: the want of a definite scientific standard by which the effectiveness of preparations could be assayed and measured, and the want of concentrated preparations of the chemical principles of the various ovarian hormones. Both these desiderata have now been attained.

Isolation of the Ovarian Endocrines

The possibility of a scientific endocrine therapy of ovarian disorders may be said to date from 1923, when Allen and Doisy invented a reliable method of standardization of the oestrogenic principles of the ovary. The original rat unit, which was the amount of material required to induce oestrus in an ovariectomized sexually mature rat of given weight, is now being supplanted by the international unit, which is defined as the activity contained in 0.0001 mg. of the chemically pure ovarian follicular hormone. The international unit is about one-third of the Allen-Doisy rat unit. Similarly for the corpus luteum hormone a rabbit unit is used.

Doisy in 1923-4 first obtained a very active extract from the fresh follicular liquor of hog's ovaries, the oestrogenic principle contained in this he named theelin. In 1929 he and others succeeded in isolating theelin in pure crystalline form from the urine of pregnant women, and later there was isolated another active oestrogenic principle, differing slightly from theelin in chemical composition, which goes by the name of theelol. Both these preparations are now obtainable commercially, under the original names as well as under other designations. A third oestrogenic principle, which is, roughly, a benzoate of hydrogenated theelin, has now also been produced.

There is still some confusion, unfortunately, as to nomenclature. The correct chemical designations are unwieldy, and the generic term "oestrin" is often applied indiscriminately to the various oestrogenic preparations representing the ovarian follicular hormone. But the term "oestrin" is also used for the chemical nucleus of the various principles. From the practical point of view one has to be content to order by the various trade names.

At present, so far as I am aware, few or none of the really effective modern commercial preparations are made from ovarian substance itself. Enormous doses of the ovarian principle are necessary to produce an effect, and to get these enormous doses in sufficient concentration material such as pregnancy urine or placenta has to be used, though there is as yet no conclusive chemical proof that oestrogenic substance from the sources named is absolutely identical with that obtained from follicular fluid. Indeed, it is only quite recently that Doisy (1935) has, for the first time, isolated a pure crystalline oestrogenic principle from the ovary itself. But it is the proved oestrogenic capacity of a preparation which really concerns us. The hormone of the corpus luteum has been isolated in pure crystalline form and has been termed "progestin," though now the name progesterone has been adopted. Preparations of it are available commercially under the name "progestin" and also under other names.

A further point of clinical importance which modern research has established is that, with a few exceptions, it is highly wasteful, if not useless, to give oestrogenic principles by the mouth. Kaufmann states that if oestrin (theelin) is given by the mouth only about one-thirtieth of the dose becomes effective. Even when given parenterally, endocrine treatment in the doses now shown to be necessary (as much as three and three-quarter million international units of oestrin may be required during a three-months course in some cases) is very expensive indeed.

The Results of Ovarian Therapy

What results are we justified in expecting from endocrine therapy in gynaecological disorders? None at all, if we persist in giving the old unstandardized tablets of ovarian or corpus luteum substance which are still on the market. There was some excuse for such preparations when concentrated, standardized forms were not available, but now they are only fit for a medical museum. But if we employ the modern standardized preparations in proper doses, and in a proper manner, we may indulge in a restrained optimism.

Kaufmann has been a pioneer in modern ovarian therapy, and it is of interest to study his results. He claims to have been, and I believe was, the first to prove that the whole menstrual cycle could be experimentally imitated in the case of a woman deprived of both ovaries. He did it by using enormous doses of both the ovarian and the corpus luteum hormones. This achievement may be regarded as a landmark, for it proved for the first time that substitution therapy, if conducted by a proper technique and by means of adequate doses, could be really effective. Starting from this point he used endocrine treatment in various other conditions, and his results may thus be summarized:

1. In Primary Amenorrhoea: Arrested Development of the Uterus, etc.

Sometimes temporary improvement, but no permanent improvement in a single case.

2. In Secondary Amenorrhoea of Endocrine Origin (Oestrin and Progestin).

Often very successful for the time being, but there is a tendency to relapse. Permanent results are, however, obtained in a proportion of the cases.

3. In Oligomenorrhoea.

Treatment is often helpful.

4. In the Menopausal Syndrome, or after Castration.

Often very successful. The follicular hormone (oestrin) only is necessary. Hormone therapy is here, in suitable cases, superior to any other form, though it must be remembered that such treatment is not necessary except in a minority of patients with menopausal trouble. Most are amenable to more ordinary measures.

5. In Uterine Haemorrhage of Ovarian Origin.

The corpus luteum hormone (progesterin or progesterone) only is used, and is very efficient.

British experience has, on the whole, confirmed Kaufmann's statements. Preparations of oestrin have been found to be especially useful also in the intense pruritus vulvae sometimes met with in castrated women or at the menopause, and Nabarro and Signy report very promising results in the treatment of vulvo-vaginitis in young children. In the latter case oestrin seems to be effective by mouth in much smaller doses than are required for other conditions.

Progestin has been found exceedingly useful in habitual miscarriage from no apparent cause—that is to say, where syphilis and organic causes can be excluded; prolan preparations are also found to be effective here. Spasmodic dysmenorrhoea and the excessive and irregular bleeding of young women have also been successfully treated by the modern corpus luteum or prolan preparations.

In spite of all this, one must stress the fact that the treatment of gynaecological disorders by hormone preparations is still in its infancy, and disappointments must on occasion be expected, even when dosage and technique are all that can be desired. Moreover, it must not be forgotten that only a minority of these cases really require endocrine treatment.

Vitamin Preparations

We used to be told, years ago, that five vitamins were essential for the maintenance of life—namely, A, B, C, D, and L.S.D.—the last being by far the most important! Of late, recent discoveries have so enlarged the number of vitamins known that we will soon have exhausted our own alphabet and may eventually have to float a loan from the Greeks. As a general rule, it may be said that, with the exception of cod-liver or halibut-liver oil, it is more physiological, and more economical, to buy our vitamins from the butcher, the greengrocer, and dairyman than from the chemist. Yet there is no doubt that in certain circumstances some of the highly concentrated vitamin preparations, especially those of A and D, are very helpful. Though a good mixed diet is not deficient in any of the vitamins, yet there are occasions when for some special purpose we wish to give larger quantities of one or other of these principles than are ordinarily contained in the diet. Moreover, owing to poverty or other causes, a good mixed diet may not easily be obtainable. It is worth remembering, however, that, even in the case of A and D, natural sources, such as the fish oils, may have an advantage over the artificially concentrated products. Even yet we do not know all there is to know about cod-liver oil, and recent researches suggest that there is some subtle difference between the vitamins contained in this and other fish oils and the artificial preparations. Nevertheless, when all is said and done, occasions do arise when these latter may be extremely useful.

I have left untouched vast tracts of my subject, but that is inevitable. If I have been able to clear up even a few points which may have been troubling the ordinary practitioner of medicine I am well content.

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ERYTHROCYANOSIS

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The condition of erythrocyanosis with which this paper is concerned figures in Continental literature under the title of "erythrocyanosis crurum puellarum," a title made still more cumbersome by the addition of the word "frigidum" in some writings. French surgeons and dermatologists describe it as "erythrocyanosis sus-malléolaire." The condition is, as these names imply, one of reddish-blue discoloration of the skin seen in the lower half of the leg in girls and young women, and especially evident in the region above the malleoli. In this respect it differs from acrocyanosis, "acro-asphyxie," which affects the most peripheral parts of the circulation—the digits, the ears, and the nose. Erythrocyanosis may affect the skin over the triceps in the arm, but seldom leads to any serious consequences in this situation. Examples of the disease in the male are very rare.

General Features

In its minor degrees the lesion in the legs is very common and trivial, but it may develop in some cases into a serious and even crippling disability. An advanced case shows the following features. The lower half of the leg, particularly on its posterior surface, is of a purplish hue, which may be uniform or marked by scattered plaques of a deeper colour. The colour is blanched by pressure, but when the pressure is released the area fills up quickly with dark blood from all sides in a way which Krogh has graphically likened to a subcutaneous lake of ink. The discoloured area is cold to the touch. The circumference of the limb is much increased by a firm, elastic infiltration of the subcutaneous tissue. This may reach very considerable dimensions, and may take the form of a thick and prominent cuff of tissue most

evident just above the malleoli and shading off higher up the leg. It produces a clumsy and evident deformity. The overlying skin is characteristic; it is stippled with small reddish points, in the centre of which is a minute keratinized focus. These are the hair follicles, enlarged and pigmented; the hair is usually absent, the "keratose pileaire" of French authors.

From time to time fairly large and very distinct indurated nodules appear in the subcutaneous tissue. When fully developed they are circular plaques 1 to 2 cm. in diameter, and are painful and very tender. On inspection the overlying skin appears a little tense and reddened, and on palpation a definite discrete induration is found, which spreads deeply into the subcutaneous tissue. Several patients have told us that they can forecast their appearance by a severe itching long before the nodules are apparent. These nodules undergo a slow resolution which at the best occupies several weeks. They often leave evidence of subcutaneous scarring, and in one of our patients, a middle-aged woman who had suffered for many years, there was a large area of thin, fibrous skin in the lower half of the posterior aspect of each leg. She stated confidently that at no time had there been any ulceration. On the other hand, in a number of cases a nodule here and there enlarges, becomes acutely inflamed, and finally bursts, leaving a small circular ulcer in the base of which is a tough, adherent slough. These ulcers are very slow to heal and often last until the beginning of summer. In the more severe cases sensations of weight and coldness in the leg, intolerable itching, and burning pain, together with the appearance of ulcers, may render the patient quite unfit for any work.

The thin, spare leg appears immune to this disease. Persons suffering from the condition are of a stout and florid build with large limbs, in which the sturdy appearance is misleading and due to excessive fat. Their general appearance is that of rude health, and Mach,¹ who gives a very good description of the lesion, states that they excite no pity because they look so healthy.

Aetiology

A study of the very extensive literature of erythrocyanosis shows that authors have been concerned mainly with two different views in aetiology. According to some