PROPRIETARY REMEDIES, WITH SPECIAL REFERENCE TO HYPNOTICS*

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Proprietary remedies far outnumber official ones. Their definition, which presents some difficulty, is given by the American Medical Association as:

"Any chemical, drug, or similar preparation used in the treatment of diseases, if such article is protected against free competition as to name, product, composition, or process of manufacture by secrecy, patent, or copyright, or by any other means."

Many are substances of genuine merit, but the dubious devices employed by certain proprietors to promote the sale of their particular drugs engender feelings of resentment and suspicion among the medical profession in respect of all. The following blatant methods are in common use: the application of a registered name to a pharmacopoeial drug and its sale to the public in an attractive packing; the exploitation of the mystery of vitamins and radium as a means of selling mixtures containing, in addition, analgesic, stimulant, or aperient drugs; and the obfuscation of the medical man himself by plausible, pseudo-scientific trade literature adorned by fantastic chemical nomenclature.

The present object, however, is to extol the virtues of ethical remedies, not to discuss the black sheep of pharmaceutical exploitation. One of the greatest tributes paid to those who devise new drugs and patent them is the official adoption of drugs of proprietary origin in later editions of the *British Pharmacopoeia*. Methyl sulphonal was patented in 1888 as a sulphonal derivative of greater solubility and speedier hypnotic action than the parent substance. It was sold as trional, but soon found its way not only into the *British Pharmacopoeia*, but into those of Belgium, Holland, America, and Japan. Barbitone itself had a similar origin, and was introduced under the registered name veronal in 1903. Nowadays it is official in the leading pharmacopoeias throughout the world. Soluble barbitone, patented in 1904 as medinal (Schering), is enjoying a similar career, and has just been introduced into the new 1932 edition of the *B.P.* So it has been with heroin, dionine, atophan, stovaine, and a host of other products.

RESEARCH BY COMMERCIAL FIRMS

Facilities for pharmacological research in our universities and medical schools are very limited indeed. During the last half-century attention has been focused on anatomy, physiology, and pathology, but pharmacology and experimental therapeutics have been neglected, although they have a direct vocational bearing and supply the true link between the academic knowledge of the non-practising medical scientist and the everyday needs of the busy practitioner. This neglect is largely responsible for the mental dissociation which takes place between knowledge acquired laboriously in undergraduate days and that used directly for the benefit of the patient. The legitimate demand of the practitioner for new tools and drugs has in the past largely been met by firms interested financially in the sale of their products. Large sums have been diverted from their dividends into the channels of research. It would be more in keeping with the dignity and traditions of the profession if independent pharmacological research could be endowed in our medical schools and universities sufficiently well to enable us to

make our own discoveries. We ought not to be under so great an obligation to the manufacturers of proprietary remedies in this matter. The discriminating work on the active principles of ergot carried out by Sir Henry Dale and his co-workers in the Wellcome Research Laboratories^{2,3,4,5} is an outstanding example of important advances made under the direct aegis of commercial concerns. Such firms exert a powerful influence on post-graduate teaching. It is a good policy to interview travellers from important drug houses and scan the literature with which they burden the breakfast table. In this way there can be acquired much useful knowledge which is not imparted in the lecture rooms and wards. The simplicity and reiteration of their statements register in memory and practice more effectively than does logical exposition before learned societies or in scientific journals.

Vegetable mucilages, such as those of linseed, psyllium, and ispaghula, have long been employed in gastro-enterology, but as a class they never enjoyed any great vogue in this country until some difficulties of administration were overcome and house-to-house instruction in their properties undertaken by Messrs. Napp and Co. in their efforts to sell a particular brand of dried mucilage as normacol. The practical importance of this type of therapy is now common knowledge throughout the profession.

The physical process of adsorption had been known and widely used in general commerce and in chemical research long before the century began. It is highly improbable, however, that in 1914 even one practitioner in a thousand realized that it could be applied advantageously in the treatment of alimentary conditions. Now, thanks largely to the educational value of trade literature, adsorption by china clay and kindred products is made use of daily by a large proportion of the profession to purify infected and putrescing material in the stomach and intestines. It has become a fundamental therapeutic principle in dealing with intestinal toxæmia and poisoning from contaminated food.

Palatability, elegance, convenience, and painlessness all call for a type of research for which the medical man has little time to spare, but they are essential to success and the special concern of those who manufacture under patents and registered names. It is useless to prescribe unless the patient will consume. The tablet has made the midday dose so easy that the business man and the patient who is out all day have now no excuse for omitting it. The earlier forms of injectable iron made up to prescription provoked a local reaction so painful as to prohibit their use. Proprietary solutions, such as Messrs. Roberts and Co.'s ferrigen or Fraisse's ferruginous serum, were painless and essential. Now at last a painless injectable iron preparation has been introduced in the new *B.P.*

VALUE OF A "BRAND" NAME

Sale under a brand name has much to be said in its favour. The quality even of *B.P.* products sold by large firms under their brand name is often maintained by systematic tests of a far more discriminating nature than those laid down in the *Pharmacopoeia*. Until a year ago medicinal paraffin could be sold as conforming to *B.P.* standards even if its specific gravity was as low as 0.860. Samples of light oils of this nature were on sale in all parts of the country, but they were useless for lubrication

* Based on addresses read before the Kent Branch and the Kensington Division of the British Medical Association.

If sodium is added to the "B" nucleus without disturbing the essential ring formation the product becomes soluble. This confers greater speed in action—for example, barbitone sodium or medinal is far more soluble and quicker in action than simple barbitone or veronal. Solubility also makes it possible for one to inject the drug. Most of the basal anaesthetics are sodium compounds—for example, soneryl is a sleep-producer. Soneryl sodium, being more soluble, can be injected as a basal anaesthetic. Amytal sodium, evipan sodium, pernocton, and nembutal itself are all compounds of this class.

In the stage of intoxication which precedes narcosis susceptible patients show excitement. Almost everyone must on occasion have given soluble barbitone and produced a state of excitement which has hindered rather than promoted sleep. The preventive for such trouble is a preliminary dose of bromide. In certain cases, therefore, bromine has been introduced into the barbiturate nucleus—for example, noctal; pernocton.

AMIDOPYRINE AND BARBITURATES

Attempts to confer pain-relieving qualities on the barbiturates have not been very successful. The closest approaches to a solution which have been made up to the present are the association of a barbiturate nucleus with amidopyrine in Pfeiffer's compound, used in veramon, and the linkage with a member of the morphine group in didial and codeonal. Amidopyrine, a derivative of antipyrine, is well known under the registered name of pyramidon, and appears to possess greater analgesic properties than antipyrine itself or other members of the simple coal-tar group. Its pain-relieving powers are enhanced by admixture with a simple hypnotic, possibly because the latter diminishes the patient's anticipation of pain. This fact has been made use of in a popular modern series of pain-relieving mixtures which fall outside the Dangerous Drugs Acts (see Table II).

TABLE II.—Analgesics Based on Amidopyrine

Allonal	=	Amidopyrine	+ a barbiturate
Asciatine	=	"	+ butyl chloral
Cibalgin	=	"	+ a barbiturate
Compral	=	"	+ a urethane
Optalidon	=	"	+ a barbiturate
Somnosal	=	"	+ bromural
Veramon	=	"	+ barbitone
Veropyron	=	"	+ barbitone

In each case pain relief is due to amidopyrine combined either mechanically or molecularly with a simple hypnotic. A barbitone derivative with pain-relieving qualities in its own right is still to be found.

DERIVATIVES OF MORPHINE

Research has also been active among the derivatives of morphine with the object of securing pain relief without causing either constipation or addiction. The bowel difficulty has largely been overcome, but it has proved impossible to dissociate addiction from the analgesic qualities of these drugs. All substances of this group with any powerful control over pain are therefore still controlled by the Dangerous Drugs Acts. They may be placed in two therapeutic groups: those akin to morphine in their control of pain, and those resembling codeine in that their analgesic properties are feeble and their utility confined to the relief of cough (Table III).

TABLE III.—Morphine and Codeine Group

For Pain:	For Cough:
Acetone	Codeine or methyl morphine
Dicodid	Dionine or ethyl morphine
Dilaudid	Eucodine
Eukodol	Paracodin
Heroin and morphine	(Free from the D.D.A., but
(All under the D.D.A. regulation)	of no real utility as anal-
	gesics)

HYPNOTIC CREDENTIALS

The credentials of every new hypnotic should be carefully examined before a single dose is prescribed.

Is It a Barbiturate?

No one who is familiar with Sir William Willcox's¹⁰ work on this group of drugs can fail to realize the great harm which can follow the repeated use of many members of this class. Unfortunately, the manufacturer often cloaks the description of his drug with complex chemical terms which mean nothing to most of us. For example, dial is diallyl barbituric acid, and if so described is recognizable at once as a barbitone derivative. It can also be correctly described as diallyl-malonyl-urea. It must be remembered, therefore, that all malonyl-ureas are barbitone derivatives. If, however, the firm which markets this drug describes it as 2, 4, 6, trioxo-5-diallyl-pyrimidine, what can we do? The description is correct, but none except a research chemist specializing in the organic branch would recognize it as a barbiturate.

There are many urea derivatives other than the malonyl-ureas, and some are first-class hypnotics. They are not barbiturates and are particularly useful for patients with idiosyncrasies and for those who have become habituated to barbiturates (see Table IV).

TABLE IV.—Urea Derivatives (Not Barbiturates)

1. Carbromal, now B.P. and sold as adalin, nyctal, planadalin, uradal.
2. Bromural or dormigene
3. Sedormid

The Margin of Safety

The actual potency does not concern us much. It is just as easy to give five grains of one drug as one grain of a more potent one. The point of practical importance is the margin of safety between the hypnotic dose and the lethal one. This is represented by the ratio M.L.D./M.Th.D. The higher this figure the safer the drug. Quoting from the literature:¹⁷ luminal is 1.3; barbitone 1.6; soneryl, nembutal, and phanodorm, 2.4; dial, 2.5; evipan, 5. From this it would appear that it is not very safe to employ luminal in full hypnotic doses, although in sedative or anti-epileptic dosage it is free from immediate risk.

Duration of Sleep to be Expected

The effect of a sleeping draught should last many hours, but die away before morning. For a basal anaesthetic a much shorter duration is desirable. Quoting once more from available literature:—Human therapeutic dosage: evipan sodium intravenous lasts twenty minutes, and evipan by mouth two hours. Rats¹ with coma dosage: nembutal, four and a half hours; pernocton, five hours; amyral, six to thirty hours; luminal, dial, and allurate, eighteen to twenty-four hours; barbitone, eighteen to thirty-six hours. The duration of narcosis produced by the dial group lies between the evanescent basal anaesthetics and that of drowsy barbitone itself. As judged by these two considerations of safety and duration alone the basal anaesthetics of choice are evipan and nembutal. Practical experience appears to justify this conclusion.

How Quickly will the Patient go to Sleep?

It is impossible to foretell whether preliminary excitement will occur during the intoxication phase or not. The question can only be answered after therapeutic trial. The speed with which hypnosis will be induced

can, however, be surmised from the solubility of the substance. If a quick effect is desired a barbiturate containing sodium should be used.

Hang-over and Cumulation

The questions of hang-over and cumulation depend upon the completeness with which the drug is dealt with by excretion or detoxication over periods of eight and twenty-four hours respectively. They are best determined by therapeutic trial, but the laboratory data are of interest. Barbiturates meet with various fates after ingestion. Some are re-excreted, others are broken down, and others disappear mysteriously. Frethwurst, Halberkann, and Reiche⁶ could recover 75 per cent. of a given dose of barbitone from the urine, 65 per cent. of pernocton, only 30 per cent. of dial, between 10 and 40 per cent. of luminal, and no amytal or neonal at all. Evipan is said to be metabolized completely in a few hours. Clearly urine analysis alone does not yield any reliable index of the probability of hang-over. Cumulation is more easily determined, especially if the drug is recoverable in part from the urine. Barbitone is known to be a serious offender, and the following analyses^{8, 9} furnish the chemical explanation of the defect: only 8 per cent. appears in the urine in the first twelve hours; 20 per cent. in the first twenty-four; 36 per cent. in the first forty-eight; and traces can be found for as long as nine days after a single dose.

A number of other important points are only decided after the drug has come into wide use and experience has accumulated. Toxic effects may arise, due not so much to the cumulation of the drug in the tissues as to the summation of its effect on the tissues. Mental impairment and the motor paralysis following luminal are examples of this kind of trouble. The range of possible idiosyncrasies and the degree to which the patient is exposed to the risks of addiction are only discernible after the drug has been in use for years.

TABLE V.—Some Hypnotic Mixtures

Alepsal	= Phenobarbital, belladonna, and caffeine
Beatol	= Barbitone, valerian, and hyoscyamus
Belladenal	= Phenobarbital and the alkaloids of belladonna
Bromidia	= Chloral bromide and hyoscyamus
Bromovalerianate	= Chloral bromides and valerian
Brosedan	= Bromide and yeast
Indonal	= Barbitone and cannabis indica
Neurinase	= Soluble barbitone and valerian
Theogardenal	= Butobarbital and theobromine
Veronidia	= Soluble barbitone and passion flower

PRACTICAL SUGGESTIONS

1. The rejection for general use of any proprietary preparation which is merely a mixture of old familiar friends. It may be appropriate when circumstances are exceptional.

2. The rejection of any proprietary preparation exploiting the pain-relieving properties of amidopyrine and other coal-tar analgesics. These parent substances can be prescribed from the B.P., with the addition, if desirable, of the hypnotic of individual choice. Similar rules could be formulated on a rational basis in all branches of this subject of the proprietaries. If universally adopted they would spare the memory a great and daily increasing burden.

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BASAL ANAESTHETICS AND ALLIED SUBSTANCES

THEIR USE AND MISUSE *

BY

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The group of anaesthetic agents to which a great deal of attention has been drawn in the last few years are solids which are administered to the patient in solution in water. They provide a contrast to the well-known anaesthetic gases which are absorbed through the lungs. In this paper the attempt is made to discuss this group of non-inhalational narcotics, many of which, in view of the incomplete nature of the anaesthesia they produce when given in safe doses, have been termed "basal anaesthetics."

Although a great deal has been written on the subject by manufacturers, anaesthetists in this country have not yet offered discriminating criticism to any large extent. The medical profession and the public owe much of the progress of therapeutics in modern times to the research departments of the great drug and chemical manufacturers; but it is very necessary that judgement on the relative values of the products which these important firms offer should be dispassionate in order that, in a particular condition, the most suitable drug may be selected. To read a short excerpt quoted in the reports of a drug firm without the whole context often leads to misunderstanding of the meaning of the original author.

CHEMISTRY OF THE BARBITURATES

The substances known as sodium amytal, nembutal, pernocton, hebaral, sodium soneryl, and sodium evipan all belong to the large new group of barbiturates which modern research has elaborated. The pioneer work in basal anaesthesia by Zervas of Indianapolis with sodium amytal and by Lundy of the Mayo Clinic with sodium amytal and nembutal (which Lundy originally called embutal) should be recalled. In 1930 the present writer, together with Dr. Magill, Dr. Apperly, and Dr. Parsons, witnessed some of the work in American and Canadian clinics, and subsequently the possibilities of the various methods which are available in this interesting branch of anaesthetics have been explored by many anaesthetists in this country.

The chemistry of the barbiturates is important but somewhat obscure. For help in the compilation of the brief but by no means complete account which follows I have to thank Dr. Nierenstein of Bristol and Mr. Garfield Thomas of the Birmingham General Hospital.

About thirty years ago it was pointed out by Nebenthaue that if one prepared an isomer of urea a drug could be prepared which produced hypnotic qualities. Now urea $\text{NH}_2\text{—CO—NH}_2$ has the linkage —NH—CO— , which can be tautomerized to —N=C(OH)— . The position, however, becomes more complicated in the case of barbituric acid. Here the system $\text{—NH—CO—CH}_2\text{—}$ may tautomerize to $\text{—N=C(OH)—CH}_2\text{—}$, and thus produce a substance possessing hypnotic properties, or —NH—C(OH)=CH— may be formed, which would thus exclude the production of an hypnotic. This actually takes place in barbituric acid, which has no hypnotic properties. This tautomeric form —N=C(OH)— is termed "the Nebenthaue factor." In order to render the new linkage a stable compound, various groups such as ethyl groups replace the mobile hydrogen atoms. This opened up a new era for the

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