Observations ON THE MEDICINAL TREATMENT OF CHRONIC ARTHRITIS

(With Key Index)

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There clearly is great pleasure in variety. Drugs and potions have been furnished in profusion to combat this disease. Some are frankly quack, others vague traditions such as black snake root, poison ivy, maté, celery oil, and manaca. Others, again, are simple mixtures of well-known substances glorified by a registered name—for example, colchicum and colocynth in "Bejean's specific" and "Laville's liqueur." Apart from these, however, there are more than a hundred substances and preparations of published composition whose use is sanctioned by laboratory experiment or common prescription. A pretentious nomenclature suggests great diversity in their modes of action, but chemically they fall into a conveniently limited number of groups. It is part of the purpose of this communication to provide a guide to the formidable array, and enable the reader to see at a glance what result to expect from any particular preparation. Accepting the common view that the bulk of chronic rheumatic disorders are produced by toxin or bacterial seepage from one or more septic foci, it is possible to make a rapid survey of the therapeutic field. Lowered resistance, sensitization, perverted metabolism, and deranged endocrine secretion in many cases probably prepare the soil, but their discussion here would lead too far from the main thesis of this paper. Apart from these considerations the treatment falls under the following headings.

A. FOCUS TREATMENT

The teeth, throat, sinuses, and genito-urinary passages need surgical care and an intelligent use of antiseptics. The danger to be avoided is the infliction of chemical trauma. The stomach and intestines require careful survey that a scheme of treatment can be organized to reduce putrefaction and the harbouring of saprophytes with infective powers which enable them to penetrate^{22 23} the living tissues of the bowel wall. The chief methods are:

1. Elimination of food stasis.
2. Simplification of the diet and correction of faults in feeding and secretion with the object of reducing the amount of undigested putrescible material in the colon. A correct meal routine, efficient mastication, hydrochloric acid if needed, takadiastase, and the more potent preparations of pancreatin are important means to this end.
3. Limitation of bacterial action by antiseptics such as ichthyol salicylate, salol, or guaiacol carbonate. The last-mentioned is not antiseptic itself, but slowly liberates free guaiacol throughout the entire length of the bowel, and so exerts a mild antiseptic action at all levels. The effects of antiseptic treatment are not striking, and even the most modern products of research do not seem to achieve very much in this direction.
4. Toxin fixation by the use of an insoluble adsorbent kaolin²⁴ or charcoal capable of removing from solution toxins thrown off by bacteria and toxic proteoses produced from proteins by bacteria or perverted digestion in the gut. It is rarely possible to give sufficient charcoal to secure complete protection from these substances, but kaolin is easily taken in amounts commensurate with the mass of faecal matter to be dealt with. Most kaolin contains harmful microscopic particles of quartz and mica. For continued use it is important to employ one of the well-known proprietary brands of colloidal kaolin which have been specially freed from such deleterious matter.

B. LOCAL TREATMENT

Apart from orthopaedic methods most local treatment resolves itself into attempts to improve the circulation in the affected parts. Radiant heat, steam, hot wax and mud, and diathermy are invaluable when correctly applied. Medicinally there is a galaxy of counter-irritants, some elegant, some brutal—alcoholat de Fioraventi, oil of amber, saffrol, Chillie paste, a host of others, and the common embrocations of the *Pharmacopoeia*. The group which stands out most clearly is that of oil of wintergreen, and here the registered trade nomenclature calls for a little analysis. The advantages of wintergreen are that, in addition to its causing vasodilatation of the skin and underlying parts, it has a mild local anaesthetic action on the skin, and is absorbed, producing a general salicylate effect in mild degree.

Methyl Salicylate Group

(Syn. Oil of Wintergreen, Gaultheria Oil, Betul Oil)

Applied externally

 $C_6H_4.OH.COOC_2H_5$

Amysal	= Amyl salicylate
Bengue's balsam	= Methyl salicylate and menthol
Betul-ol	= Methyl salicylate, menthol, and chloral
Ethyl salicylate	
Glycosal	= Glyceryl monosalicylate
Mesotan	= Methoxymethylsalicylate
Methyl aspriodine	= Methyl acetyl iodosalicylate
Rhesal	= Glyceryl monosalicylate
Salen	= Ethyl and methyl glycolylsalicylate
Saliceral	= Glyceryl monosalicylate
Salit	= Borneol salicylate
Spirosal	= Ethyleneglycol monosalicylate

C. GENERAL RESISTANCE

1. Healthy surroundings, ultra-violet light, and a richly vitaminous diet are invaluable. Vitamins A and D are particularly important, and are easily given as cod-liver oil. For obese subjects, and those who have difficulty in

digesting fats, the concentrate radiostoleum is available, and with it calcium preparations, the gluconate¹⁶ or lactate, can be profitably combined.

2. Non-specific reactive therapy. A number of useful schemes have been devised:

(i) The facilitation of antibody formation by the injection of manganese.

(ii) Artificial leucocytosis by subcutaneous or intramuscular injection of suitable reagents, such as sodium nucleinate or colloidal sulphur either in a watery or an oily medium, and many other substances. The graph illustrates the effects of intramuscular colloidal sulphur on the leucocyte count. The

latter was kindly worked out for me by Dr. R. S. Bruce-Pearson.

(iii) Intravenous injections where more opportunity is given for colloid interaction—for example, cibalumin and certain bacterial emulsions such as T.A.B. Here again leucocytosis plays a part, but is certainly not the only agency at work. The method is not free from risk, and dosage is difficult to assess in terms of expected reaction in the rheumatic parts.

Other substances—for example, milk, peptone, and yatren-casein—probably act in analogous fashion, but should not be given intravenously.

D. SPECIFIC RESISTANCE

Inoculation with vaccines made from the infective bacteria of the various foci provokes pain reactions in the rheumatic areas, leads to antibody production, and is undoubtedly, on occasion, followed by definite clinical improvement. Up to the present time it has proved impossible to devise a reliable method of determining which strains should be incorporated in the vaccine. Until our knowledge is greater it is advisable to include all infective strains isolated.²⁵

E. VICIOUS CIRCLES

Results which react on causes and aggravate the original mischief are to be found in most diseases of long standing. The rheumatic group is no exception. Here subthyroidism and anaemia are the chief offenders.

(i) Subthyroidism may antedate the lesions in the joints or be collateral with them, and probably represents the effect of the focal toxins on the thyroid gland. When once established it impairs metabolism and the defence mechanism, so permitting the morbid process at foci and joints to proceed more briskly. All degrees of subthyroidism are met with, varying from the most benign to fully fledged myxoedema. Their correction by suitable doses of the dried gland has a remarkably beneficial effect on the whole syndrome.

(ii) Anaemia of the ordinary secondary type is almost universal in the more progressive forms of chronic arthritis, and may assume serious proportions; 80 per cent. haemoglobin is a common reading, but figures as low as 30 per cent. are not unknown. There is no evidence of active haemolysis, and the poverty of the blood is probably due to toxic depression of the bone marrow. It is very prejudicial, and should be corrected by iron therapy. Natural ferrous iron waters are useful, but for routine use a scale preparation or iron phosphate is effective if the bowels are acting well, and one of the strong colloidal preparations—for example, idoan—for there is any tendency to constipation.

The therapeutic field has now been represented in perspective from the viewpoint of accepted pathology, and we are in a position to deal critically with the vast array of drugs advertised for use in these conditions. They will be classified chemically, and each group assigned its appropriate place in the general scheme of treatment.

ASPIRIN

The 1,000 tons of aspirin sold in this country annually are remarkable testimony to the utility of the drug. Its outstanding effects are relief of rheumatic pains and diminution of stiffness in so far as this is not due to ankylosis or adhesions. The ultimate course of the disease does not appear to be influenced directly, but indirectly; something must be gained by enabling the patient to sleep and affording him a respite from the exhausting monotony of his pain. A portion is lost by decomposition in the stomach. The rest is disseminated very widely, and salicylates can be recovered from the joint tissues themselves, also from pathological and normal synovial fluid. Its power of relieving pain in chronic rheumatism seems almost to be specific, and is far greater than that of sodium salicylate. It is, however, exercised in a limited way in other conditions. The secret of its action is well concealed, and may involve changes in tissue tension with release of compressed vessels or nerves.

A number of observations point in this direction. Both Oswald²⁶ and Hanzlik¹⁰ have shown that aspirin alters

the permeability of certain colloid membranes. It also causes retention of fluids in the body, with a diminished urinary flow and a rise in body weight. The excess is not accommodated in the vascular system, because there is no change in the concentration of haemoglobin. It must therefore be in the cells themselves, the tissue spaces, or lymphatics.¹² Finally, idiosyncrasy to aspirin often shows itself as urticaria or generalized oedema, so that it would appear reasonable to assume that some kindred peripheral action around the joints is responsible for the loss of pain rather than to invoke a central narcotic action on pain perception in the brain.

Aspirin Group (Syn. Acetyl Salicylic Acid)

Aspro
Empirin
Genasprin

} A few registered names of brands of aspirin

Aspiphenin = Aspirin and phenacetin
Diaspirin = Succinyl salicylic acid
Metaspirine = Aspirin and caffeine
Nopirine = Aspirin, phenacetin, and caffeine
Rhofeine = Aspirin and caffeine
Aspirodine = Iodoaspirin
Novaspirin = Methylene citryl salicylic acid
Salacetol = Acetyl methyl salicylate
Sedaspirin = Bromo aspirin

Sodium cresotinate $\text{C}_6\text{H}_3 \begin{cases} \text{OH} \\ \text{COOH} \end{cases}$ (resembles aspirin in relieving the pain of chronic rheumatism)

ANTIPYRIN

The arthritic patient's demand for relief from pain has led to the development of a series of simple analgesic drugs with an admittedly central action. If derivatives of codeine and morphine are excluded most of the others will be found to be modifications of antipyrin. In this class there is great scope for mystification, because the same substance can be described in widely different chemical terms. For example, pyramidon (amidopyrin) may be referred to as dimethylaminoantipyrin or as dimethylamino-phenyl-dimethyl-isopyrazolone. Both names are correct, and although to most medical men not engaged in pharmacological or chemical research they are mere mumbo-jumbo, they carry a scientific cachet which appeals to many and which can be exploited by the vendor of drugs. The close relationship between most of the members of the series will be seen at a glance in the table appended. In addition to these a pharmacologically analogous drug phenocoll hydrochloride, a derivative of phenacetin, has been much used.

Antipyrin Group

(Syn. Phenazone, Dimethyl-oxyquinizine,
1-phenyl-2:3-dimethyl-5-pyrazolone)

Acetopyrine = Antipyrinacetosaliclate
Compral = Dimethylaminoantipyrin (that is, pyramidon) + a modified urethane hypnotic
Gardan = Dimethylaminoantipyrin (that is, pyramidon) + methylamidomethane sulphonate of antipyrin (that is, novalgin)
Melubrin = Amidomethane sulphonate of antipyrin
Novalgin = Methylamidomethane sulphonate of antipyrin
Pyramidon = Dimethylaminoantipyrin
Pyrethane = A combination of antipyrin and urethane
Salipyrin = Antipyrin salicylate

SULPHUR

It is a little difficult to see why sulphur should be so useful in modifying the course of chronic rheumatic diseases. Its use undoubtedly has received wide sanction over a long period of years. Most of it passes unchanged through the bowel and is excreted unchanged in the faeces, so that it has ample opportunity to affect the contents of the entire digestive tract. Although inert in inorganic association it readily reacts with proteins in an alkaline medium, giving rise to sulphides, which are bactericidal, irritant, and laxative, sulphuretted hydrogen, and organic sulphur compounds. All of these can be recovered from the stools.¹³ Sulphur is far more than an intestinal antiseptic. It is a detoxicating agent in virtue of its power of interacting with otherwise putrescible residues in the colon. It is a kind of scavenger modifying and destroying these protein remnants just as it destroys necrotic material and slough when packed into a contaminated wound. Varying amounts pass into the circulation, possibly as sulphides. As much as 50 per cent. of milk of sulphur may be dealt with in this manner. Up to the present, however, no systemic effects have been observed. There is no formation of sulphaemoglobin and no other evidence of free sulphide in the blood. Sulphides are active reagents and poisonous. Even small amounts would be expected to irritate the cortex or medulla. Sulphides appear in the urine, but most of the absorbed sulphur is eventually excreted fully oxidized as sulphate.

As explained before, the injection of colloidal sulphur is another matter. The fever and leucocytosis provoked in this way can be regarded as the outcome of a non-specific interaction between the colloid particles injected and those of the body fluids.

Sulphur Group

Azufrol	}	Colloidal sulphur (proprietary)
Collosol sulphur		
Dutch drops		
Oscol sulphur	}	= A preparation of sulphur, linseed oil, and turpentine
Sulfoiodol		
Sulfurion		
Thionhydrol		
Vulcase	}	Proprietary forms of colloidal sulphur

IODINE

The clinical value of iodine preparations is undoubted but limited in its scope. In the amounts prescribed its theoretical antiseptic value in gut and tissues must be negligible. One of its most pronounced features is that of storage. After a single half-gram dose of iodide, the element can be detected in the urine for forty hours, and after a short course it may take three weeks to clear the urine again.¹⁴ There are two obvious ways in which it may help the rheumatic patient. In the first place it may act indirectly by stimulating a defective thyroid gland and normalizing its secretion chemically as well as in amount. Iodine storage occurs in the thyroid gland to a greater extent than in any other tissue. The administration of iodine produces histological changes in the gland,¹⁵ raises the basal metabolic rate, and increases the functional activity of the thyroid substance as estimated by its effect on the growth of tadpoles.¹⁶

Another opportunity is afforded by the local accumulation of iodine near inflammatory foci. Not only does special concentration occur in syphilitic gummata, but also in the lipoids of tuberculous areas,⁸ and in pus and other inflammatory exudates¹⁷ where it is found as inorganic iodide. Suitable conditions are thus provided, not only for assistance through the thyroid, but for a direct action in the joints and inflammatory foci themselves, whilst the storage and slow excretion ensure steady uniform action the whole day through.

The favourite old French tincture, various colloidal forms such as iodor and collosol iodine, and the pharmacopoeial preparations of iodides and of the element itself are all in common use. There are, in addition, large numbers of iodine compounds on the market testifying to the popularity of the drug. About them, Erlenmeyer and Stein⁵ have made the sweeping generalization that all remain inert until decomposed in the tissues or the gut with the liberation of simple iodides, which are taken up again by the body colloids. They fall into two groups: those in which the iodine is combined with proteins and those in which it is linked with fats, fatty acids, and kindred substances. The former are digested in the bowel and the iodine absorbed as simple iodides, so that nothing much is gained beyond delayed absorption. The latter gain the lymphatics unchanged, and undergo preliminary distribution in a manner peculiar to themselves, attaching themselves to the body lipoids.^{1 6 20}

The lists below are by no means complete, and iodine occurs in several other combinations, as in yatren, ioda-septine, iodoxybenzoic, etc., considered in other connexions.

Iodine
(Protein Group)

Iodalbacid	
Iodalbin	With serum albumin
Iodalose	With peptone
Iodethylglycin	
Iodocasein	
Iodogelatin	
Iodoglidine	With wheat gluten
Iodone	With peptone
Iodoprotein	With albumin
Iodotannate	
Iodurase	Iodides and yeast albumin
Iolase	Iodine with yeast albumin
Seroden	With serum protein

Iodine
(Fatty Group)

Calioiben	= Calcium iodobehenate
Iodatol	= Iodized vegetable oil
Iodicin	= Calcium iodoricinoleate
Iodinol	= Iodized sesame oil
Iodipin	= Iodized sesame oil
Iodostarin	= Diiodotaririnic acid
Lipiodol	= Iodized vegetable oil
Lipiodine	= Ethyl diiodobrassicinate
Olilase	= Iodized vegetable oil
Sajodin	= Calcium iodobehenate

RADIO-ACTIVE SUBSTANCES

Radium chloride can be safely given by mouth in dose of 1/100,000 milligram several times a day for a number of weeks at a time. It is absorbed rapidly, permeates the tissues freely, and, after special storage in the liver and spleen, is eliminated through the bowel wall.^{3 27} During its stay in the body some breaks up into its degradation products known as emanation, niton, or radon, and into α rays. Radon can be detected in the air, exhaled through the lungs, and in its turn emits β and γ rays, the latter being electro-magnetic waves of decidedly shorter length than those employed in deep x -ray therapy. The γ rays are probably the factor most closely concerned in the pharmacological action of radium when taken in small doses by mouth.

The most definite effects are diuresis, lowering of the blood pressure in certain common varieties of hyperpiesia, and the provocation of local reaction around inflammatory foci. In chronic arthritis this usually takes the form of an increase of pain and swelling. With the dosage mentioned the reaction is not usually noticeable until the radium has been taken for several days. At the completion of a short course it subsides and is usually followed by a beneficial swing of the clinical pendulum in the opposite direction. A similar result can be achieved by the administration of a solution of radon or emanation in

KEY INDEX

DRUG	CHEMICAL GROUP.											
	Antipyrin	Aspirin	Cinchophen	Hexamine	Iodine		Iodoxybenzoic	Radio-active	Sulphur	Thiosinamine	Uric Acid Solvents	Wintergreen
					Protein, etc.	Lipoid, Soluble						
Acetopyrine	+											
Acitrin			+									
Agotan			+									
Amphotropin				+								
Amysal											+	
Arthritin						+						
Aspiphenin		+										
Aspriodine		+										
Aspro		+										
Atophan			+									
Atophanyl			+									
Atoquinol			+									
Azufrol								+				
Bengue's balsam											+	
Benzo-piperaz												
Betul-ol											+	
Borovertin				+								
Calculus					+						+	
Calibon						+						
Cicatricine									+			
Citarin				+								
Collosol sulphur								+				
Compral	+											
Cystamine				+								
Cystazol				+								
Cystoformin				+								
Cystopurin				+								
Diaspirin		+										
Dutch drops								+				
Empirin... ..		+										
Ethyl salicylate											+	
Fibrolysin									+			
Formalol				+								
Gardan	+											
Genasprin		+										
Glycero-piperaz										+		
Glycosal											+	
Helmitol				+								
Hetralin				+								
Hexophan			+									
Iodalbacid					+							
Iodalbin					+							
Iodalose					+							
Iodatol						+						
Iodaseptine				+								
Iodethylglycin					+							
Iodicin						+						
Iodinol						+						
Iodipin						+						
Iodocasein					+							
Iodogelatin					+							
Iodoglidine					+							
Iodolysin									+			
Iodone					+							
Iodoprotein					+							
Iodostarin						+						
Iodotannate					+							
Iodurase					+							
Iolase					+							
Lipiodol					+							

DRUG	CHEMICAL GROUP.											
	Antipyrin	Aspirin	Cinchophen	Hexamine	Iodine		Iodoxybenzoic	Radio-active	Sulphur	Thiosinamine	Uric Acid Solvents	Wintergreen
					Protein, etc.	Lipoid, Soluble						
Lipiodine					+							
Losan												
Lycetol			+								+	
Lysidine												
Melubrin	+										+	
Mesothorium												
Mesotan												+
Metaspirine		+										
Methyl aspriodine												+
Metramine				+								
Mirion				+								
Neocinchophen			+									
Nopirine		+										
Novalgin	+											
Novaspirin		+										
Novatophan			+									
Oliolase					+							
Oscol sulphur									+			
Piperazine											+	
Piperidine											+	
Pyramidon	+											
Pyrethane	+											
Quinic acid											+	
Quinophan			+									
Radon water									+			
Rhesal												+
Rhodallin										+		
Rhofeine		+										
Sajodin					+							
Salacetol		+										
Salen												+
Saliceral												+
Salicyl-piperaz											+	
Salipyrin	+											
Salit												+
Scleradium									+			
Sedaspirin		+										
Seroden					+							
Sidonal											+	
Sodium cresotinate		+										
Solulol											+	
Spirosal												+
Sulfoiodol											+	
Sulfurion											+	
Thionhydrol											+	
Thyminic acid												+
Tiodine... ..										+		
Tolysin			+									
Ura'ysol				+							+	
Uraseptine				+							+	
Urazin											+	
Uricedin											+	
Urodonal									+		+	
Urogenine									+		+	
Uro-hexoid									+		+	
Urosin... ..									+		+	
Vesalvine B.									+			
Vesalvine S.									+			
Vulcase										+		

water, but the effect is less steady and more transient, partly because of rapid elimination of radon through the lungs, and partly because radon has a very short life, being fairly completely dissipated in a few days' time.

Agents conveniently at our disposal and arranged in increasing order of potency are as follows:

Spa waters containing radon.

Water which has been allowed to stand in a container in which radium ore is incorporated. This also relies on its radon content.

Solutions of radon produced under controlled laboratory conditions from pure radium salts, as at the Radium Institute.

Scleradium, stated to contain a standardized amount of radium chloride itself in a fairly large saline tablet.

Other radio-active substances also are available. Thorium, used extensively in the manufacture of incandescent gas mantles, undergoes slow and continuous molecular degradation, giving rise to mesothorium, which gives off γ rays whilst further degradation is taking place. Mesothorium is isolated as a by-product in the manufacture of gas mantles, and the yearly output was at one time estimated as equivalent to about $1/2$ gram of radium in terms of γ radiation, but its average life is only a few years in contrast to the 2,600 years of radium. Mesothorium is supplied in solutions of various strengths up to 2 micrograms of the bromide per c.cm.

It is important to remember that solutions of radon must be fresh, because they become inactive in less than a week. Mesothorium keeps for several years, and radium indefinitely.

THIOSINAMINE

This substance was introduced by Hebra and Unna in 1892. It does not dissolve at all freely in water. Simple soluble modifications such as sodio salicylate (fibrolysin) are therefore used instead. It provokes a widespread reaction with metabolic effects, evidenced by fatty degeneration of parenchymatous organs and increased elimination of nitrogen. Clinically the reaction produces malaise and pyrexia, and appears in some cases to be followed by the resolution of low-grade indolent localized infections, with a diminution in the fibrous and other chronic inflammatory tissues which surround them. A list of preparations is given below. In this connexion contramine should be mentioned. Its chemical relationship to this group will be seen by comparing its published structural formula with that of thiosinamine.

It is also a reactive drug, and is supposed to produce its effect by physical interaction with the body colloids rather than by simple chemical means. Our knowledge of the mode of action of these admittedly potent drugs is still extremely scanty, and it would appear rash to use them unless the patient can be kept under close medical observation.

Thiosinamine Group

(Syn. Allyl Sulphocarbamide, Allyl thio urea)

Cicatricine	=	Thiosinamine and antipyrin
Fibrolysin	=	Thiosinamine sodio salicylate
Iodolysin	=	Iodine derivative of thiosinamine
Rhodallin	=	Thiosinamine
Tiodine	=	Thiosinamine ethyl iodide

IODOXYBENZOIC ACID

This substance and the related compounds iodosobenzoic and iodobenzoic acids have been known to pharmacologists for many years, but the group was not introduced into

clinical medicine until 1926, when Young and Youmans published a series of cases treated with ortho-iodoxybenzoates. Given by mouth iodoxybenzoates cause sweating and a certain amount of epigastric discomfort, followed by relief of joint pain. It is more usual to administer it intravenously as a solution of its sodium or ammonium salt, the latter being preferable because of the decided tendency of the sodium salt to cause local thrombosis. It is bactericidal to staphylococci and streptococci, even in the presence of serum,² but it seems unlikely that this property is responsible for the clinical effects following intravenous injection. Used in this way it provokes a polymorphonuclear leucocytosis, and in experimental animals there is an increase in the formation of antibodies.¹⁵ The immediate clinical effect is a smart reaction, with sweating, fever, nausea, and abdominal pain. Relief of joint pain and associated muscle spasm commonly follows, but is not usually very lasting. The unpleasantness of the reaction is a serious drawback to the use of the drug. Like thiosinamine, its effects are somewhat akin to those of non-specific reactive therapy.

Arthritin = Ammonium ortho-iodoxybenzoate

CINCHOPHEN

Nicolaier and Dohrn introduced this substance in 1908. Its popularity probably depends entirely on its pain-relieving qualities, which in acute rheumatic fever rival those of the salicylates themselves. Although aspirin is the most useful analgesic in chronic arthritis the antipyrin and cinchophen groups are keen competitors.

Scientific attention has been keenly focused on the increased excretion of uric acid which follows the use of this substance. The percentage of uric acid in the blood falls at the same time,^{7 21} and suggests that cinchophen increases the permeability of the kidney to urates and so facilitates their excretion. The power of cinchophen to relieve pain is not confined, however, to those chronic arthritides with high blood uric acid values, and is, on the whole, more conspicuous in chronic infective arthritis than in true gout. Clinically there is little justification for its use if pain can be controlled in other ways. It does not seem to have any direct effect on the final result, and on quite a number of occasions jaundice, with serious degenerative changes in the liver, has followed the use of cinchophen and its derivatives. It is only fair to add that there is no evidence that the liver is attacked in every case; indeed, Graham (1926) showed that, even after long courses of the drug, liver function as measured by the levulose curve was usually unaffected. Nevertheless the incidence of acute liver changes in this connexion is too significant to pass unnoticed.

Cinchophen Group

(Syn. Phenoquin, Phenyl Cinchoninic Acid, Phenylquinoline-carboxylic Acid)

Acitrin	=	Ethyl ester of cinchophen
Agotan	=	Cinchophen
Atophan	=	Cinchophen
Atophanyl	=	Sodium cinchophen and sodium salicylate
Atoquinol	=	Allylcinchophen
Hexophan	=	Oxycinchophen
Losan	=	Sodium bicarbonate and cinchophen
Neocinchophen	=	Ethyl ester of methylcinchophen
Novatophan	=	Ethyl ester of methylcinchophen
Quinophan	=	Cinchophen
Tolysin	=	Ethyl ester of methylcinchophen

HEXAMINE

This drug is not often prescribed alone in chronic rheumatic conditions, but being an ingredient in a number of popular proprietary mixtures, such as urodonal, it must claim some attention here. When used in chronic arthritis the usual intention is to exploit its solvent action on uric acid, not to employ it as an antiseptic for the urine. The consideration is of theoretical interest only, and it is impossible to detect any fall in the uric acid content of the blood or any rise in the daily excretion even when full dosage is employed. Its clinical influence on the symptoms or the course of the disease is not apparent. It might conceivably produce a beneficial effect by liberating traces of formalin at the infected joint areas and primary foci. The concentration of formalin liberated from hexamine is determined by the acidity of the surrounding medium, and is not quite zero even at the point of neutrality to litmus. It can be shown that at a reaction corresponding to that of blood about 1/2 per cent. is split up into formalin after a few hours, and at the reaction of asphyxial blood the figure reaches almost 1 per cent.^{4 11 20} Local CO₂ tension and acidity are definitely higher around areas of inflammation than elsewhere, so that some support is given to the idea that free formalin is produced in these situations. Whatever formalin may be liberated in this way is bound at once by protein, and loses its antiseptic properties. Nevertheless through this means it might indirectly influence the course of the disease beneficially. The reaction by which formalin is liberated is a balanced one. The prompt removal of formalin by protein fixation should therefore lead to the continuous production of more and more formalin as long as any hexamine remains. It must be admitted, however, that large doses of hexamine can be injected intravenously without provoking any obvious disturbances such as those associated with colloid shock or following the introduction of thiosinamine or iodoxybenzoates, and that most of it can be recovered again from the urine.

Hexamine Group

(Syn. Urotropine, Formin, Formamine, Hexamethylenamine, Hexamethylene tetramine, Methenamine)

Cystamine	}	Two of many proprietary brands of hexamine
Metramine		
Amphotropin	=	Hexamine camphorate
Borovertin	=	Hexamine triborate
Cystazol	=	Hexamine sodio benzoate
Cystoformin	=	Modified hexamine
Cystopurin	=	Hexamine sodium acetate
Formalol	=	Hexamine anhydro methylene citrate
Helmitol	=	Hexamine anhydro methylene citrate
Hetralin	=	Hexamine resorcin
Iodaseptine	=	Iodobenzo methyl hexamine
Mirion	=	Iodo-hexamine
Uralysol	=	Hexamine (+ helmitol, lysidine, and thyminic acid)
Uraseptine	=	Hexamine (+ helmitol, piperazine, lithium, and sodium benzoate)
Urodonal	=	Hexamine (+ lysidine, sidonal, and sodium bicarbonate)
Urogenine	=	Hexamine (+ piperazine, lithium, and sodium benzoate)
Uro-hexoid	=	Hexamine (+ lithium benzoate)
Vesalvine B.	=	Hexamine benzoate
Vesalvine S.	=	Hexamine salicylate
Citarin	=	Sodium anhydro methylene citrate (liberates formalin easily, and can be mentioned here, although not actually a derivative of hexamine)

PIPERAZINE AND OTHER URIC ACID SOLVENTS

Piperazine,^{9 22} when added to urine, increases its ability to dissolve uric acid. Lithium salts increase the solvent action of water for uric acid, but in the serum and urine the excess of sodium nullifies the effect completely. It

is entirely improbable that under clinical conditions these substances affect the urates in the tissues or the blood in any way. Even if it can ever be proved that they are able to exert some such action it will still remain to be shown that the patient benefits from the change. Piperidine and thyminic acid belong to the same pharmacological group. The clinical effects, if any, of using this class of substance in the treatment of chronic arthritis are quite imperceptible.

Uric Acid Solvent Group
(Excluding Hexamine)

Benzo-piperaz	=	Piperazine benzoate
Calcusal	=	Piperidine para sulphamine benzoate
Glycero-piperaz	=	Piperazine glycerophosphate
Lycetol	=	Dimethylpiperazine tartrate
Lysidine	=	Ethyleneethenyldiamine (also in uralysol and urodonal)
Piperazine	=	Diethylenediamine (also in uraseptine and urogenine)
Piperidine	=	Hexahydro tetraoxy benzoic acid
Quinic acid	=	Piperazine salicylate
Salicyl-piperaz	=	Piperazine quinate (also in urodonal)
Sidonal	=	Thyminic acid (a nucleoprotein derivative also in uralysol)
Solurol	=	
Thyminic acid	=	
Urazine	=	Piperazinecitrosalicylate
Uricedin	=	Lithium succinate
Urosin	=	Lithium quinate

With few exceptions the relatively inert lithium salts have been omitted, and no special mention is made of saline aperients or mineral base preparations. The lists are admittedly far from complete, but most of the preparations which have obtained a vogue in recent years have been included.

With so many substances at his disposal the medical man, bewildered, may well pause before giving his patient any positive advice at all. A critical survey of every organ and system is essential, and in making a therapeutic plan it is useful not only to keep in mind the balanced scheme of treatment outlined in the earlier part of this paper, but to decide whether the chief effort should be centred on the joints themselves, the septic foci, the digestive tract, the endocrines, general resistance, non-specific reactive therapy, or an attempt made to raise specific resistance to particular bacteria by vaccines. Clinical observation usually indicates clearly where the greatest advantage is to be secured. Suitable medicinal agents can then be selected with confidence. Revision will be needed from time to time to make good an advantage or to pass from one gain to the next objective, and little by little, with care and patience, what seemed at first impossible will be achieved.

Much care has been taken to ensure the accuracy of the chemical statements made, and I am greatly indebted to Professor C. S. Gibson for acting as censor in this matter. I should nevertheless welcome communications from any manufacturers who consider that their products have been misrepresented from the chemical point of view, and from any practitioner who has had outstanding success in the treatment of chronic arthritis with any drug omitted from the discussion or schedules.

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CLOSED DRAINAGE IN THE TREATMENT OF EMPYEMA

WITH A REPORT OF FORTY-TWO CASES IN INFANCY AND CHILDHOOD*

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Hippocrates taught that in cases of empyema the operation to drain away the purulent effusion should not be performed before the fifteenth day after the onset of the illness. He also advocated irrigation of the cavity. His teachings therefore foreshadowed two principles in the modern treatment of this disease.

PRINCIPLES OF MODERN TREATMENT

Delay before Operating.—Empyema is not to be regarded as a surgical emergency requiring operation as soon as it is diagnosed. The necessity of waiting until the adhesions between the lung and the chest wall are sufficiently firm to prevent the lung from pulling away from the chest when the thorax is opened is well recognized. It is also advisable in most cases to wait until the pneumonic process has subsided before continuous drainage of the empyema is undertaken, the pus being removed by repeated aspiration until such time as the pneumonia has resolved. All the cases here reported have been aspirated at least once—depending on the nature of the condition. In cases of empyema due to the streptococcus, effusions into the pleural cavity are prone to occur at an early date, and firm adhesions between the visceral and parietal pleurae do not take place as readily as when the infecting organism is the pneumococcus. Where the empyema is caused by the streptococcus, therefore, aspiration is persisted in longer than where it is due to the pneumococcus. In the latter case we feel that adhesions between the lung and the chest wall are sufficiently firm to prevent collapse of the lung after thick pus has been present for one week; while in the case of the streptococcus we consider that we must wait from two to three weeks for the above desired result. Here it may be well to point out that in aspirating pus from the pleural cavity, the utmost care should be taken to prevent air from entering the thorax. It is always very disappointing for a surgeon to find that an exploratory puncture has been performed, and that

air has been allowed to enter the chest, with additional lung collapse and spread of infection.

Irrigation.—The second principle employed by Hippocrates was that of irrigation. While he washed out the cavity with wine and oil "to cleanse the surface of the lung," we use Dakin's solution to overcome the infection, to liquefy the masses of fibrin so that they will pass out through the catheter, and to soften the exudate which covers the surface of the lung and impedes its expansion.

Application of Negative Pressure.—The third principle—which Hippocrates did not employ—is the application of negative pressure to assist in expanding the lung and thus obliterate the cavity. Forty years ago Beulau inserted a catheter through a trocar into the thorax, drained off the fluid, and applied negative pressure drainage. Since that time the closed method of drainage in empyema has had some advocates and many adverse critics. Notwithstanding the advantages claimed by those who used the closed method, it has been slow in coming into general use. After a personal experience with the closed drainage combined with irrigation of the cavity with Dakin's solution in more than fifty cases of empyema, I have found that this way of treating the condition is so much better that I have abandoned the open method. I therefore take this opportunity of focusing attention on this subject, in the hope that those who have not hitherto given this method a trial will do so.

APPARATUS

I wish also to call attention to a very simple apparatus which I have employed for this form of treatment, as

Illustrating closed drainage of empyema.—To irrigate the cavity the rubber tube connecting the Y glass connexion with bottle A is clamped, after which the clamp is removed from the tube connecting the Y with the container for Dakin's solution; when the abscess cavity is filled the solution is clamped off and the clamp between the Y connexion and bottle A removed, allowing the solution to drain off by suction into bottle A. To remove the solution accumulated in bottle A, clamp both rubber tubes leading from the glass connexions in the cork; the cork may then be withdrawn and the bottle emptied without disturbing the siphon.

I feel that one reason why more surgeons have not given the method a thorough trial is the complicated nature of the apparatus described from time to time for its

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