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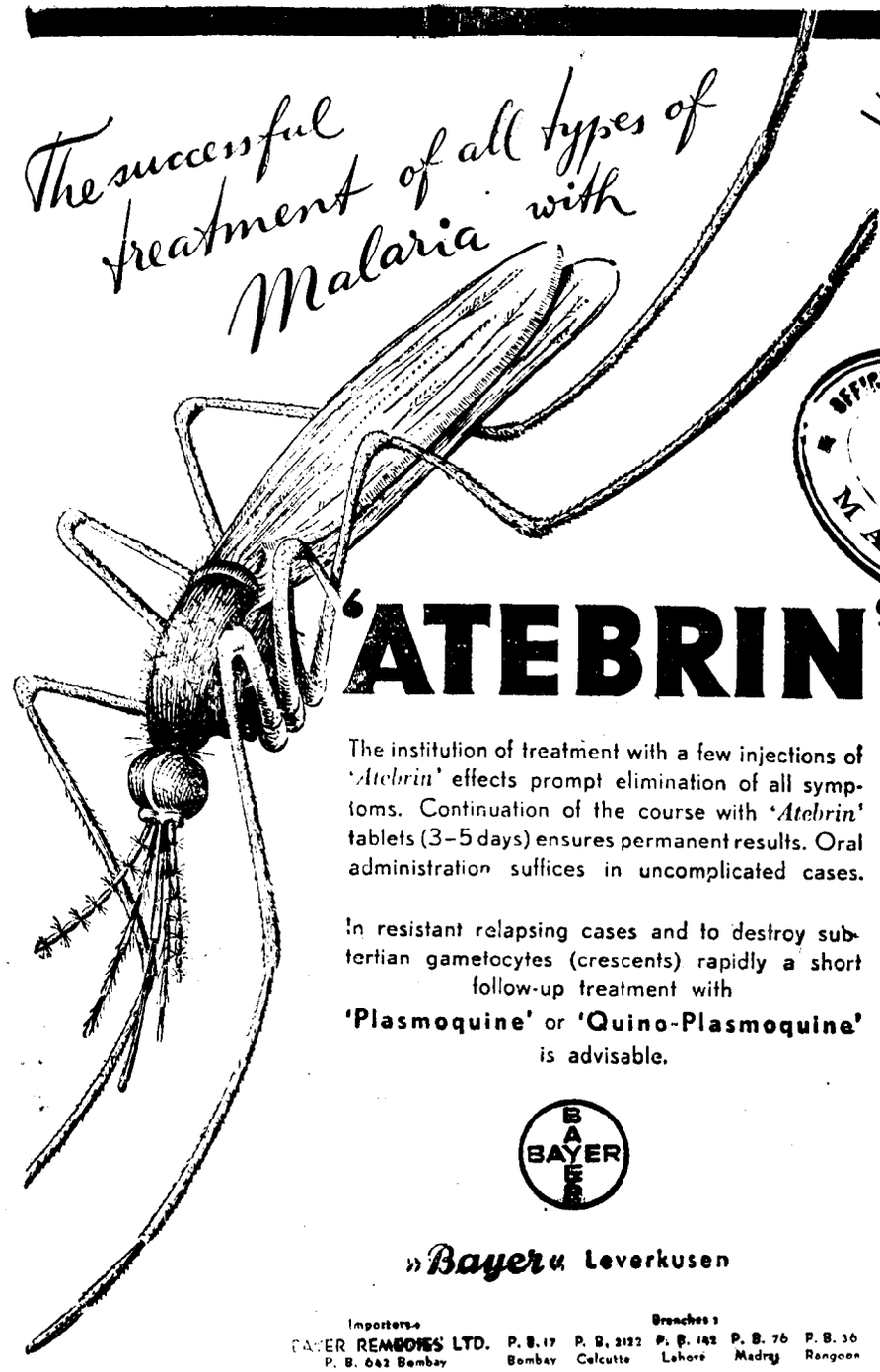

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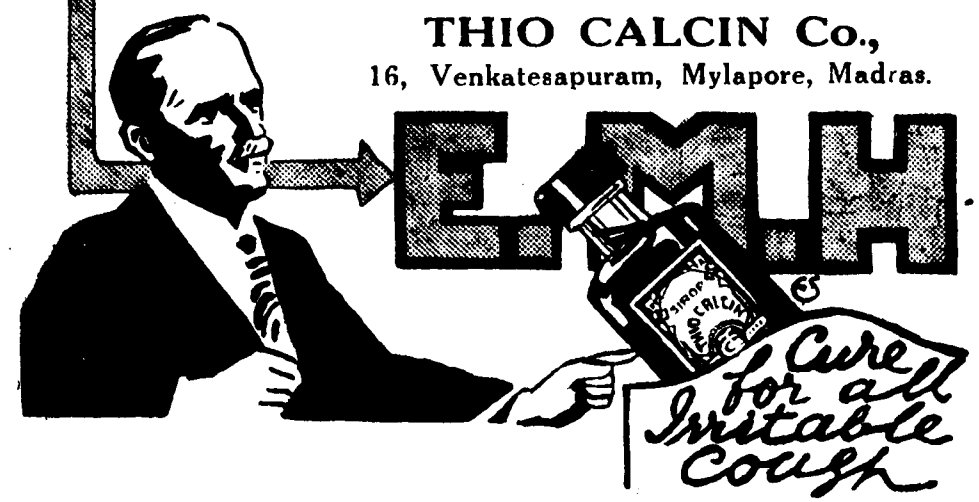

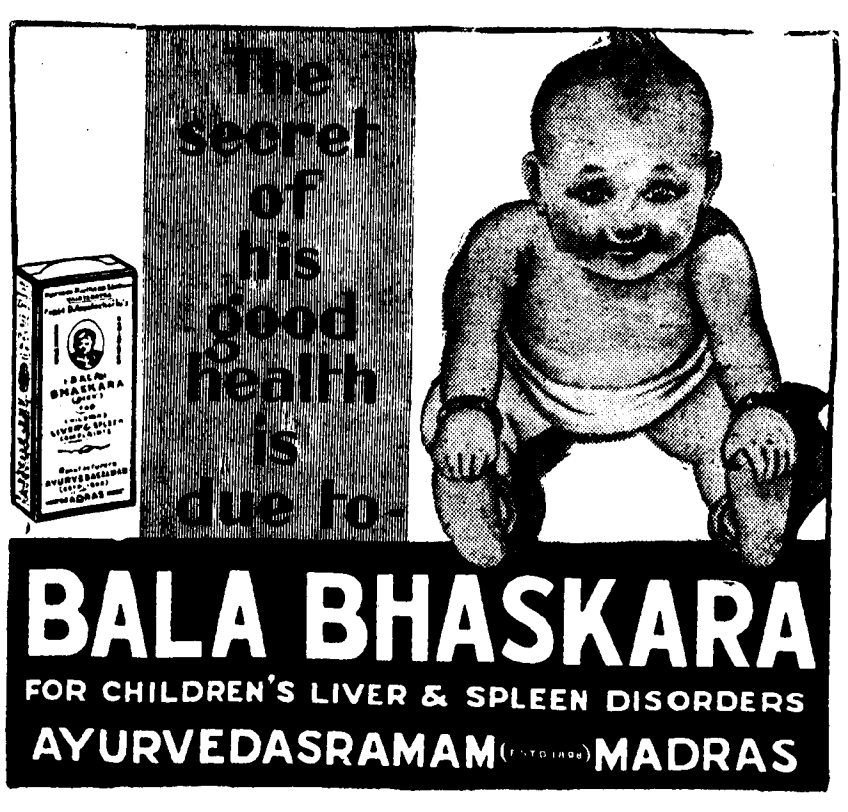

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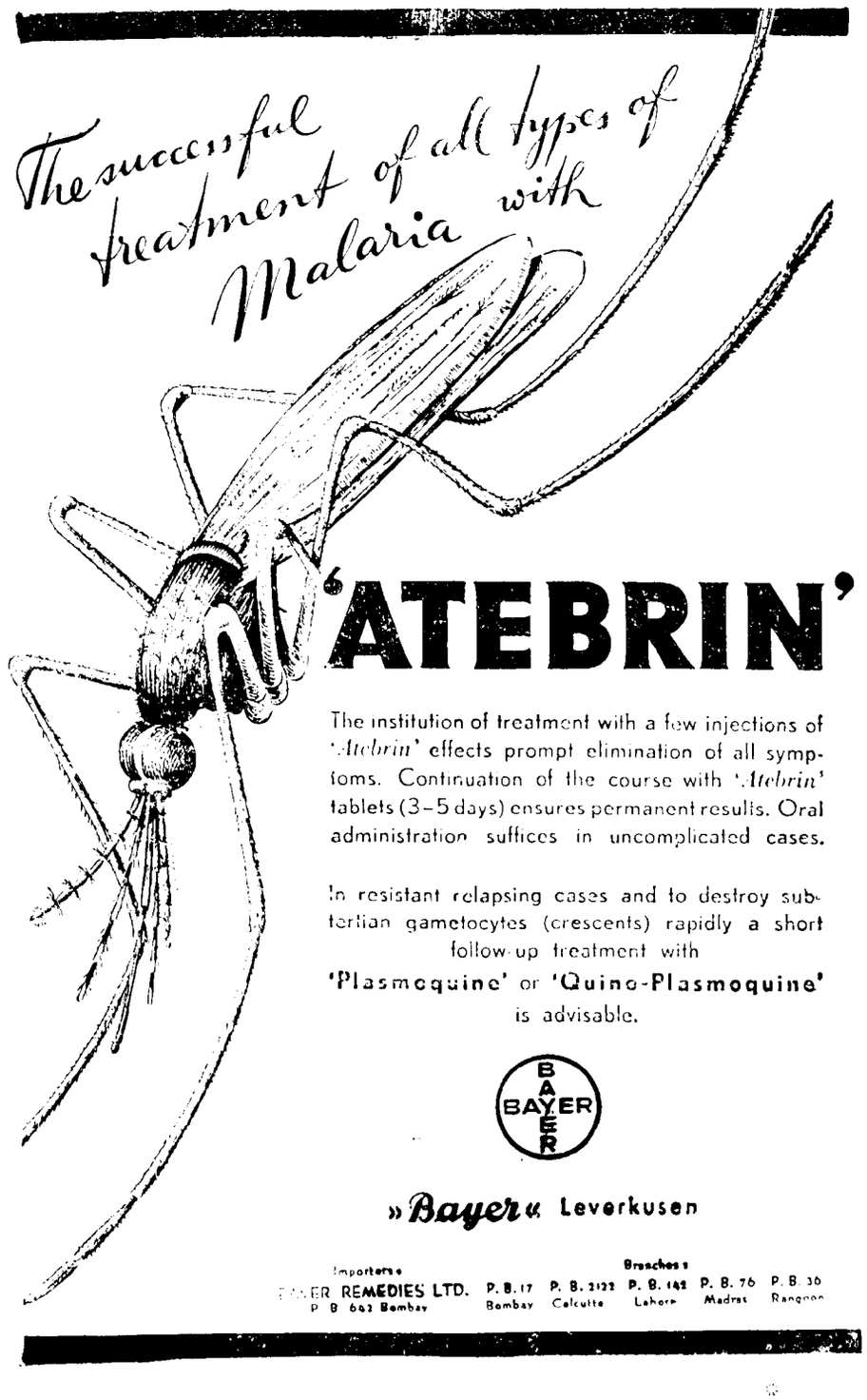

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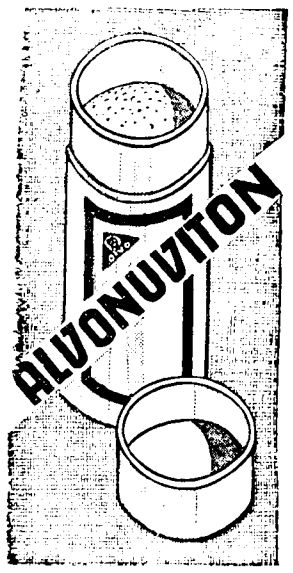

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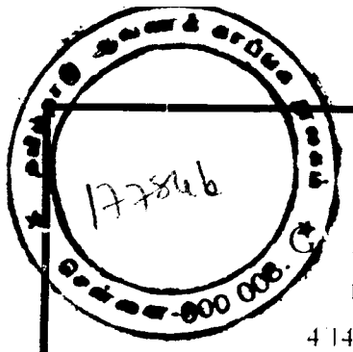

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HEMOGONON is sold in bottles of 10½ fl. ozs. The usual dose for Adults is 3 tablespoonfuls daily, while to children 2-3 teaspoonfuls are usually given.

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Vol. VI] MAY 1939 [No. 5

Treatment of Pneumonia with M. & B. 693.

(*Clinical Journal, May 1939*)

A DISCUSSION on recent advances in the treatment of pneumonia took place at the Royal Society of Medicine, with special reference to the use of M. & B. 693. Dr. L. F. H. Whithy said that its efficacy had been fully confirmed. Provided the patient could live for 24 hours and retain some 5 gm. the chance of success was greatly increased whatever the day of the disease on which the treatment began. The scheme of dosage was usually 4 to 5 gm. in the first 24 hours, and then 3 gm. daily to a total of 25 gm. Patients treated on the fifth day and afterwards required not more than 15 gm. to produce a crisis and cure. Administration should be continued for about 5 days, even though the temperature dropped, for premature discontinuance was always followed by an exacerbation. Mild infections required almost the same dose as acute and fulminating ones. The basic indications for the drug were coccal infections. It had no action on influenza. Its chief disadvantage was vomiting, which occurred in about 30 per cent of patients. It often subsided in 24 hours, and to tide the patient over this period the method of administration could be varied. A 2 per cent solution of the sodium salt was suitable for rectal administration.

Prof. A. Fleming said that M. & B. 693 did not seem to kill the pneumococcus, which presumably was killed by the natural defences. It therefore seemed desirable to increase

these. The mortality might be still further reduced if patients were immunized when the drug was given. Some experiments seemed to show that the pneumococcus might develop a fastness to the drug.

Dr. W. F. Gaisford had treated in hospital with M. & B. 693 between 600 and 700 patients, of which 400 had lobar pneumonia. The total mortality dropped from about 23 to between 6 and 7 per cent. The mortality in patients over 50 dropped from 17 to 1·6 per cent. Temperature returned to normal within 48 hours of beginning the treatment. Continuance of pyrexia after a drop indicated either a complication, or an organism that was not pneumococcus. There seemed to be no alteration in the rate of resolution. A rapid improvement in the general condition took place after the fall in temperature. The mental depression characteristic of the sulphanilamide group was observed in a number of cases, but lasted only a short time. Complications due to the drug had been mild. A number of rashes were seen, similar to those caused by sulphanilamide, but less severe. In allergic patients these rashes became urticarial; they were independent of the dosage and disappeared in a few days. Cyanosis was observed, but ceased to cause anxiety. An existing cyanysis was not a contra-indication to the use of the drug. Very young patients did not vomit, but in adults this complication was important. If a patient vomited, the next dose should be given by a different route. Vomiting was rarely so persistent as to prevent a sufficient dose from being retained.

Sulphanilamide Therapy in Arthritis

(*The Practitioner, April 1939*)

The value of sulphanilamide therapy when instituted in the early stage of gonococcal arthritis, i.e. before joint destruction has taken place, is shown by a report on eighteen cases given by H. C. Coggeshall and W. Bauer (New England Journal of Medicine, January 19, 1939). Except in one case, in which an initial dose of 90 c.cm. of a 2·5 per cent solution was given intramuscularly, the sulphanilamide was given by mouth in dosage of ¾ grain per lb. body weight or 1 gm. per 20 lb. body weight. Some patients received half the calculated dose initially and again four hours later, followed by one-sixth of the calculated dose every four hours day and night: this was found the most satisfactory method of administration for maintaining a constant blood-sulphanilamide level. The therapy was continued over a period of two weeks or more, and in some cases half or one-third the calculated daily amount was continued for another two weeks. Sodium bicarbonate in equal dose was given at the same time as the sulphanilamide in order to lessen gastric disturbances. With correct dosage signs of improvement were noted within forty-eight to seventy-two hours of the beginning of treatment. The genito-urinary tract was free of gonococci after the third day of treatment, and synovial fluid became sterile within the first forty-eight to seventy-two hours. All the patients showed improvement in the arthritic symptoms: complete cure was obtained in nine patients, five of whom regained 100 per cent joint function and in three cases recalcification and new bone formation was shown on X-Ray examination. Some secondary reactions in the form of nausea, skin eruptions, cynosis, leucopenia, acidosis, and rise in temperature were noted, but no case of severe secondary anæmia occurred. The authors recommend the administration of large doses over a shorter period as the most likely way of reducing toxic manifestation: those observed in the present series were, however, not serious, and quickly responded to appropriate treatment, i.e. cessation of sulphanilamide and the forcing of fluids (5,000 c.cm. the first day). Ten cases of rheumatoid arthritis failed to respond satisfactorily to sulphanilamide therapy. Although the doses used were large. No changes in the erythrocyte sedimentation rate occurred and only one patient showed improvement in the joint symptoms.

Cocoanut oil derivatives as Bactericides in the Operating Room

(*The Practitioner, Feb. 1939*)

In addition to germicidal powers, the ideal bactericide must possess a low toxicity, power of penetration with resultant good skin tolerance, lack of odour and staining properties, and a marked detergent action. The germicidal powers of cocoanut oil derivatives have been recognized for some years, and the substitution of these compounds for the saponifying base in compound solution of cresol has been found to increase the phenol coefficient of the solution 50 to 100 per cent. By incorporation into benzyl-ammonium chloride compounds, the bactericidal activity of the cocoanut oil derivatives is increased and the irritative properties of the oils mitigated. C. W. Walter (Surgery, Gynecology and Obstetrics, Nov. 1938) has investigated the properties of a mixture of cocoanut oil derivatives (high molecular alkyl-dimethyl-benzyl-ammonium cholorides) and tested their efficiency by animal and human experiment, as well as in the operating theatre, and on the basis of the results obtained he recommends the use of this compound for the following purpose. *Skin disinfection*: the operative field is scrubbed for one minute with soap (10 per cent. aqeous suspension of equal parts of cocoanut and olive oil soap) and water, until a stiff white lather is produced; this lather is removed by shaving and the skin rinsed with fresh tap-water and dried. The procedure is carried out, when possible, at least twelve hours before the operation, and no dressing is applied to the site during the interval. On the operating table, using the method of swabbing along the contemplated line of incision and working in concentric strokes from the centre of the field to the periphery, the site of operation is scrubbed with three changes of sponges saturated with a 1 : 1000 aqueous compound, and alternated with three changes of sponges soaked in 70 per cent. alcohol, denatured with oil of cajuput tinted with eosin. After the operation

silver foil is applied to the incision and a sterile gauze dressing secured to the skin by zinc oxide adhesive plaster. No case of skin irritation due to this treatment occurred in the author's series, even when the dressings were left untouched for five to seven days, or even fourteen. When mechanical cleansing is difficult, a wet dressing of 1 : 1000 aquæous solution should be applied two hours before operation, and when the site is exposed in the theatre the skin should be moistened with 1 : 1000 tincture of the compound before applying the towels. Suitable dye can be added to stain the area if desired. *Disinfection of the hands*: After three to five minutes scrubbing with soap and hot water (preferably with cocoanut-oil soap), a stiff lather being maintained for three minutes, the hands and arms are immersed in a 1 : 1000 tincture (50 per cent. chemically pure alcohol and 5 per cent. chemically pure acetone) for two minutes; all soap must be thoroughly rinsed off before immersion. The bactericide should be replenished every day and the solution discarded after it has been used 150 times. *Glove basins*: One litre of 1 : 5000 solution is sufficient fluid for glove disinfection, the same solution being used to rinse the gloves during the operation. Fresh solution must be used for each operation. *Instruments:* The cleansing of instruments and supplies which do not withstand sterilization by heat is carried out by submersion in a 1 : 1000 aqueous solution for thirty minutes, after previous cleansing. No damage is caused by the solution to optical instruments, rubber goods, shellac catheters, paraffin mesh, or guttapercha, but it cannot be used for storing metal instruments.

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Adrenalin, Morphine and Aspirin in Asthma

(*Advance Therapy, April 1939*)

Duke (Jour. Amer. Med. Assoc., Aug. 20, 1938) states that adrenalin is the drug of choice in bronchial asthma of children and young adults. It acts promptly and effectively, is harmless and nonhabit-forming. The author warns against the use of morphine in cases where adrenalin has failed to act and symptoms of cynosis, dyspnœa, orthopnœa and tachycardia are manifest, as morphine lessens the cough reflex, and so increases the obstruction. It may also depress the respiratory centre in the brain and act allergically causing an acute reaction. In severe intractable asthma adrenalin may be used intravenously well diluted with the patient's blood in the syringe. Morphine (¼-½ gr. hypo.) is, however, highly efficacious in cardiac asthma of older persons with high blood pressure, nephritis or aortic regurgitation. Aspirin is effective in bronchial asthma but carefully eliminated.

The Trichinopoly District Medical Association

(*Registered*)

A monthly meeting of the Trichinopoly Dist. Medical Association was held at 5 p.m. on Thursday the 20th April, 1939 at Govt. Headquarters Hospital, Trichinopoly, when Dr. R. G. Cochrane, Medical Officer, Lady Willingdon Leper Settlement, Chingleput, delivered an interesting lecture on "Leprosy." About 40 doctors were present. Dr. V. Sankararama Iyer, R. M. O., Govt. Hospital, Trichinopoly, was At Home and Lt. Col., N. K. Bal, M. C., I. M. S., Dist. Medical Officer, Trichinopoly, presided.

The lecturer said that Leprosy was a disease known throughout the world for thousands of years. The Europeans, the Anglo-Indians and the Mongolians are the most susceptible races, while the Indians and Africans are more resistant and tend less often to show the more virulent forms of the disease. In spite of the above fact Leprosy was practically wiped out of Europe three centuries back by the strict enforcement of segregation. The widespread incidence of the disease in India and Africa was a bar to its eradication by segregation. Moreover all types of Leprosy are not infective and do not require strict segregation. It is not possible to isolate the large number of leprosy patients found in the country but much could be done by creating a sense of responsibility in the patients themselves from carrying the infection to others by confining themselves to their own habitation, and giving them separate bedding, room, utensils etc. A great deal could also be done by preventing children up to the age of 18 from coming in contact with patients in the infectious stages.

He said that the word 'leper' should be eliminated from the medical parlance as the word had a stigma and meant one to be shunned. No patient suffering from leprosy need be treated as an unapproachable and none needed to be treated as

untouchables, as infection usually takes place after long contact with an open type of case. (An open case is in which bacilli can be demonstrated, by the usual methods of examination in the skin and mucous membrane of the nose.)

The two types of the disease were the nerve type and the lepromatous types. The nerve type was characterised by thickened nerves and anaesthetic patches. Anaesthesia should be elicited with cotton wool or feather and even such a procedure was not definite in the case of patches on the face, as the skin of the face has an abundant nerve supply. Very often thickening of the nerve cannot be elicited but decolourisation and erythema round the patch was more characteristic. The tuberculoid type—a sub-type of neural leprosy—was due to sensitisation of the skin to the bacilli which were often found in smears from the thickened skin. The nasal mucous membrane was rarely the seat of primary infection. The treatment was quite simple and as old as the disease itself: i. e., chaulmoogra oil in one form or other. Either hydnocreol or the esters 75 : 25 of olive oil and 4 of creasote may be used. Intravenous injections should be avoided, the remedy should be given subcutaneously beginning with ½ c. c. and going to 5 c. c. twice a week, i. e. 10 c. c. a week, injecting not more than 3 c. c. in a place.

Intradermal injections are also very useful in the affected lesions. The usual method is to raise about 6 to 12 wheals with one c.c., each wheal being about ½ to one inch from the other. The maximum dose for intradermal medication is 5 c.c. in adults and 3 c.c. in children. In children the total dosage (both subcutaneous and intradermal) should not exceed an aggregate of more than 1½ c.c. per every ten pounds body weight. Lepromatous cases are not only difficult to treat and require to be treated for a long period of time but sometimes lepra reaction is seen. The characteristics of this reaction are (1) rose spot nodules, (2) fever, and (3) evidence of fresh lesions. This reaction is easily controlled by the administration of potassium antimony tartrate intravenously or the pentavalent preparation Fouadin. The dosage of potassium antimony tartrate is 0.02 to 0.04 gms. in 2 c. c. water every other day intravenously or 2 c. c. Fouadin intramuscularly.

As in all chronic diseases the earlier the treatment is begun the quicker will be the result, and this in lepromatous cases usually takes from six months to two years.

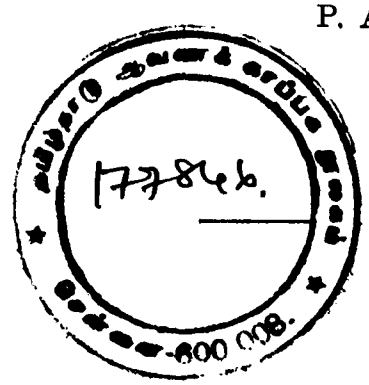
Hygienic living, plenty of fresh air and sun light go a great way in the prevention and cure of the disease. Diet is only an accessory element though lack of calcium and protein tended to diminish resistance to the disease. Wheat, hand-pound rice, vegetables, milk and milk products aid in preventing and healing the disease.

He paid a tribute to the Govt. of Madras and especially to Hon'ble Dr. T. S. S. Rajan, Minister for Public Health, for the interest they were taking in the prevention and treatment of the disease. He impressed upon all the necessity for medical men correctly to diagnose early cases and give systematic treatment until the disease was arrested. He then demonstrated a few cases and showed a number of magic lantern slides showing the disease in various stages and the response to treatment given.

Dr. P. A. S. Raghayan, the Secretary, in proposing a vote of thanks to the President, host and the lecturer said that eminent men like Dr. Cochrane who took a living interest in the eradication of the disease and identified themselves wholeheartedly with the work, were doing a great service to the country, and as such it was no wonder that the Popular Government was taking a keen interest in their work. He also thanked the Municipal Health Officer Dr. T. C. John, L. R. C. P. & S., for lending the use of the magic lantern.

The meeting terminated at a late hour.

P. A. S. RAGHAVAN,
Secretary.



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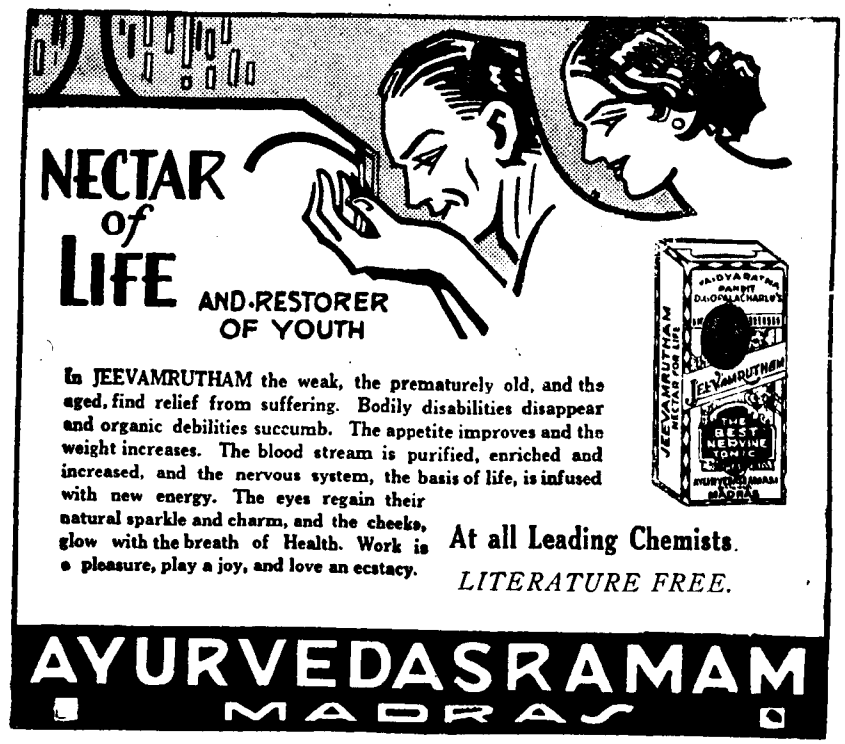

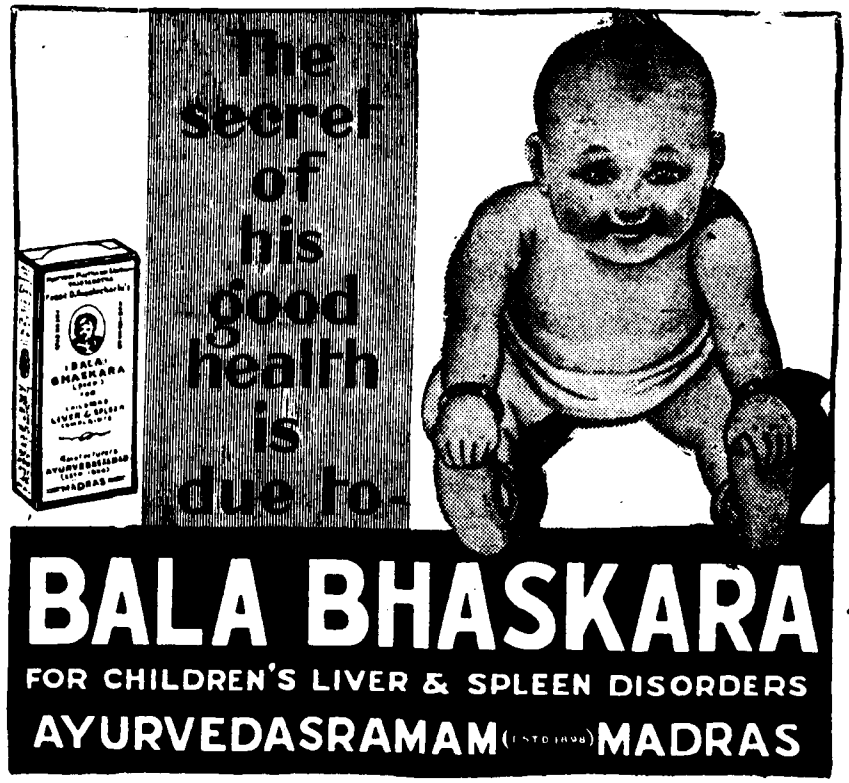

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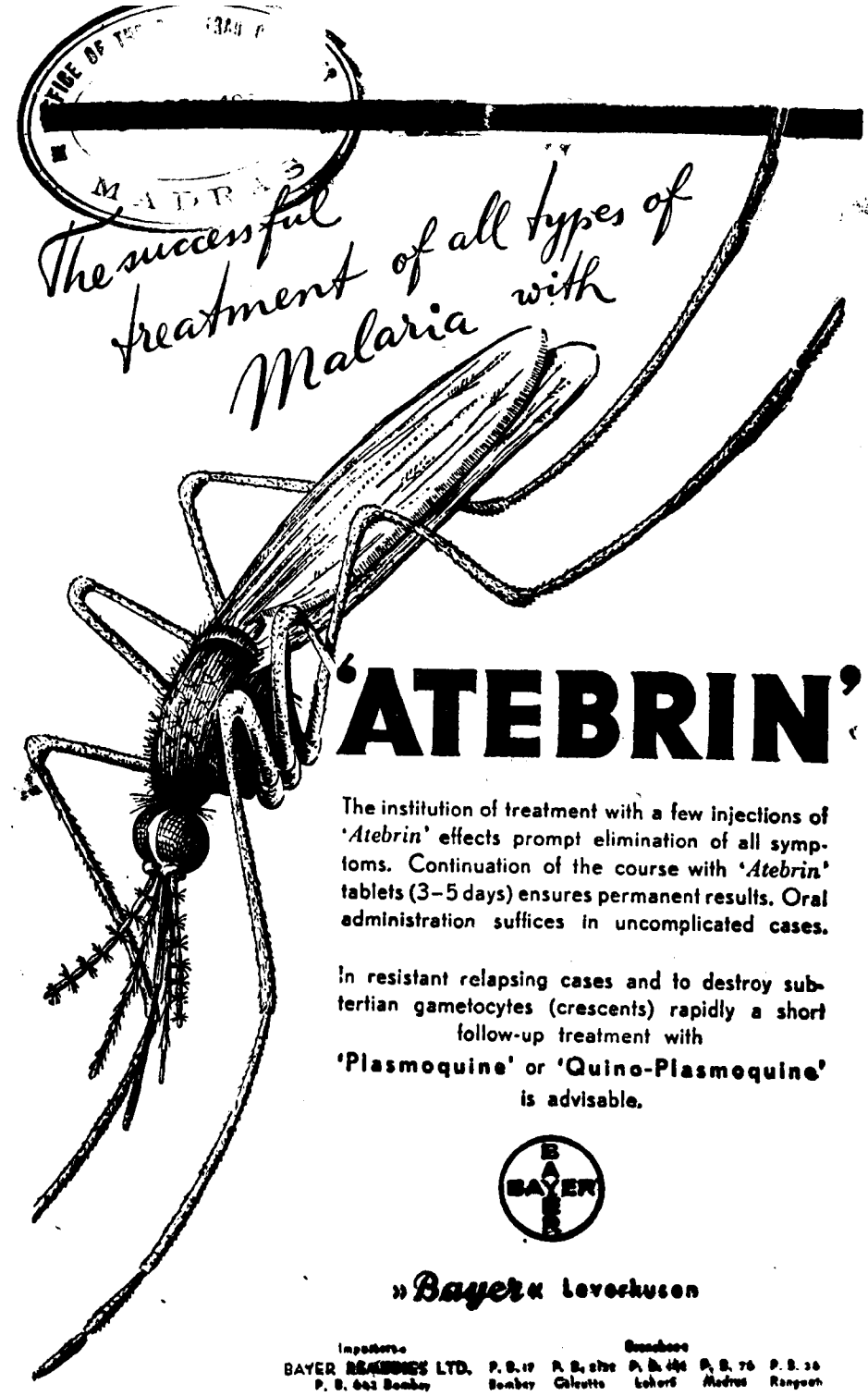

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Vol. VI] JUNE 1939 [No. 6

Drug Therapy *vs.* Commercial Pharmacology

BY

DR. J. C. DAVID

MY subject for to-day's talk has been chosen with the main object of bringing before you as forcibly as I can the fight against empiricism in drug therapy. Chemotherapy is a mere restricted term. But a great number of therapeutic remedies are promiscuously classified under this head in the many pamphlets and advertisements either couched in pseudo-scientific language or in which the claims are made on the basis of experimental trials without the check of proper controls. This latter type of therapy, I term *Commercial Pharmacology*—which in itself has become a highly complicated and specialised art. I hesitate to use the term 'science' in this connection. The history of drug therapy is almost lost in antiquity; and it is indeed not at all strange that an implicit and child-like faith in the efficacy of drug treatment for the cure of all the ills we are heir to exist even to-day in the minds of the general public. This belief, erroneous though it be, may have to be pandered to, by the medical practitioner, to some extent. For after all, what both the physician and the patient want is a cure and relief from suffering. The first criterion in the cure of a patient is to get his confidence. Once this is obtained by the physician, half the cure is finished. Seeing that this implicit faith in drugs exists in the human mind, the

Lecture delivered at the Meeting of Trichinopoly District Medical Association held on 24-6-1939 at Karur, Trichy District.

Jc

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doctor will go a long way in the treatment, if he prescribes some drug even in cases where his better judgment would indicate that drugs are unnecessary. In such cases, what we term *placebos* are prescribed. But such placebos need not be unnecessarily costly and need not also be in the form of some patent medicine, which mostly goes to enrich the foreign drug exploiter and to impoverish the people of this land.

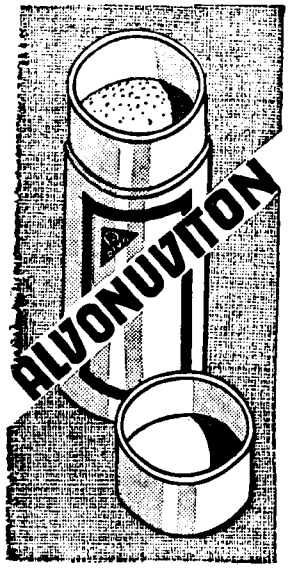
What I am up against is the implicit belief which many practitioners place on the literature so attractively printed on the back of blotting papers which they get so frequently and regularly by post, to the great profit of the druggist and the needless waste of the patient's money, which he can ill afford. What is needed is a *healthy scepticism* which will hesitate to take for gospel truth the claims made by the medical advertiser. Pharmacology is now taught as an experimental science, based on the student's knowledge of physiology. In such a method of teaching the student is constantly encouraged to think for himself as to why and how a given drug gives rise to certain effects. Pharmacology is based, as already mentioned, on physiology and chemistry is one of its main supports. Any claim made for the action of a drug must be capable of being analysed chemically and physiologically and only when the results of such analysis support the claims made, can such a drug be accepted. Many practitioners make the same mistake number of times or give a particular drug under uncontrolled circumstances and call it experience. Unless experience can be measured by physical, chemical, physiological and even psychological terms, it is of as little value as gossip in a court of law. When a student is trained to exhibit such healthy scepticism and his critical faculties are so directed, it is our hope that when he qualifies and goes out into the stress of medical practice he will continue to be as critical of the enormous literature of wonderful panaceæ and cure-alls which he encounters day after day. It is my duty to commend to all of you here present this critical attitude in the assessment of the value of therapeutic remedies.

I must not be misunderstood of being what is called a Therapeutic Nihilist or condemning all the remedies which are outside the pale of the Pharmacopœia. There are quite a

number of reputed firms which have done a great deal towards the advancement of chemotherapy. As a matter of fact, most of the recent advances in chemotherapy have come from the laboratories of some of the leading pharmaceutical houses. Sometimes a new drug with a definite action is put up. In other cases, reputed brands which are free from the suspicion of adulteration are available for the prescription of medical practitioners and some firms put up elegant preparations of known formulæ of familiar drugs which have an advantage over similar prescriptions which can be filled by the ordinary dispensing chemist. Such helps in therapeutics should not be scorned, where the proper indication exists because such remedies have gone through the mill and have obtained the stamp of approbation of independent critics.

In this country we are up against still another evil—that of the innumerable remedies marketed and prescribed under the guise of the so-called indigenous systems of medicine. I have the greatest respect for the pioneering efforts of these systems at an age when the present civilisation of the West was nonexistent. But while respect and veneration for the work and times of our ancestors should naturally form part of the body politic, a blind belief in the infallibility of the hoary past acts more as a millstone round our necks and tends to drown our better instincts. It is an insult to the brain that God has given to us for proper use and assiduous improvement. Unfortunately any sort of healthy criticism of the customs or manners or religious or pseudo-religious or pseudo-scientific beliefs of our country brings forth only abuse, and there all activity stops.

Medical ethics forbid us to advertise our wares or our abilities. But no such inhibitions exist for the indigenous practitioner. Hence his remedies are always before the eye of the general public; and this added to a veneration for all that is Indian, confirms its faith in the efficacy of such quack remedies. One is surprised at the gross lack of critical spirit in otherwise highly educated people who do not hesitate to give testimonials which are widely published. In this connection I would like to point out how, in many such instances, the testimonials are obtained. I know of a medical colleague, whose wife was very ill from T. B. in spite of all that medical science



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could do for her. He was persuaded against his better judgment, to go to one of these indigenous luminaries who specialised in the treatment of this disease and whose advertisements along with testimonials appeared in the daily papers. When he went to get the medicine, he was kept waiting for hours, at the end of which, the specialist gave the medicine for a week's treatment. At the end of the week some little progress was reported and a testimonial was obtained before the doses for the next week were handed over. In a disease like tuberculosis, with its ups and downs, any alteration of treatment or environment might work some change for the better for a few days and at this juncture the testimonial is obtained. The patient in the case I mention died a little later. Though the testimonial duly appeared in the papers, the final sequel was not told the public.

Even in scientific journals, we often find a tendency to extol the virtues of a new drug without proper control as the result of observations on a few cases; but there is not seen a correspondingly eager attempt to faithfully report failures. But a critical mind will easily spot the fallacies in such deductions. Quack remedies have a successful sale mostly in such diseases like leprosy, tuberculosis, venereal diseases etc. in which the symptoms have their ups and downs and in which a temporary improvement can very easily be pointed out to hoodwink the gullible public. I do not for a moment maintain that none of the remedies used by the indigenous systems of medicine is of any use. I dare say that a few gems are bound to be buried in the cartloads of indigenous remedies of known and unknown formulæ. Sometimes there is one real active principle which is almost lost in the 101 other materials which are supposed to go into the making of the prescription. Some really good remedies which might be known to a few are not published and such knowledge dies with these few. A few missionary outlook is sadly wanting in our country however much we might deny it. In the West, a new discovery is always published and everybody has an opportunity of benefitting by it. Even if some remedies are patented, the formulae are soon known and the knowledge is passed on to posterity. But conditions in our country are quite different. I would like to believe that there are some really good remedies in Ayurveda. But dogged and

continued research by pharmacologists and others have brought little to light. A tidy sum of money is awaiting the man who could demonstrate a snake cure to the satisfaction of the Director of the Haffkin Institute, Bombay. But although we hear stories of miraculous cures from the bite of poisonous snakes, nobody has so far succeeded in demonstrating a foolproof snake bite cure.

One often hears statements made at public meetings by some mushroom politicians of the glories of the past and the necessity for synthesising the best in the East and the West into one medical science which will be peculiarly suited to the constitution of the Indian body. I am prepared to admit that this country had a glorious past—though I have no personal knowledge of it. The statement that the indigenous drugs are peculiarly suited to the constitution of the Indian is an untruth which does not need contradiction by any intelligent person. The idea of synthesising the Indian and Western systems of medicine into one whole is a ludicrous one which makes me laugh and reminds me of the story in Pickwick Papers about the article on "Chinese Metaphysics" which a correspondent in the Eatenswill Gazette contributed to that esteemed journal. When Mr. Pickwick asked how on earth the man could get hold of materials to write an article on such an abstruse subject, Mr. Potts, the editor, exclaimed "Why, that is easy enough. My correspondent looked up China and Metaphysics in the Encyclopædia Brittanica and combined both into one article." This illustration will readily show the absurdity of any such idea of combining the so-called allopathy and ayurveda into one homogeneous whole.

I have a deep-rooted aversion for the name *Allopathy* as applied to the scientific medicine of today. This name was originally applied to the heroic treatment advocated by Gregory who died in 1821. He believed in bloodletting, emetics and purgatives. The name is derived from two Greek words meaning "other sufferings". Hahnemann who lived about the same time revolted against this unsatisfactory system. Although we might not agree with many of Hahnemann's fundamental ideas, it is his merit to have conceived the idea of an experimental science of pharmacology based on observations of the

actions of drugs on normal individuals. Hahnemann's system of Homeopathy soon drifted into absurdities. From 1829 onwards he advocated the administration of all drugs at the 30th potency, which corresponds to a concentration of 1 part in 10^{60} which works out at a content of one molecule of drug in a sphere with a circumference equal to the orbit of Neptune. Homeopathy and allopathy were equally devoid of any scientific basis, and it must be admitted that the former did less damage in practice. Homeopathic methods gave scope for the natural defence mechanism of the body, while allopathic methods were calculated to kill even without the aid of disease. Modern therapeutics has inherited from allopathy the knowledge of many useful drugs and from homeopathy the knowledge of the remarkable powers the body possesses of healing itself. Homeopathy also has stressed the importance of other measures like dieting, nursing etc. apart from drugs. Modern therapeutics is an inductive science based on observation and it has nothing in common with any of the past or present systems of medicine based on authority. So the application of the terms Allopathy to modern scientific medicine is a misnomer. Science knows no boundaries of race, country or religion. But scientific medicine is more cumbered than any other science with pseudo-scientific rivals. There are several reasons for this. Firstly therapeutics was placed on a scientific basis only about two generations ago, and popular beliefs are usually about this distance behind scientific knowledge.

Secondly, it is more difficult to make adequately controlled observations in therapeutics than in any other science, and hence it is very difficult to provide rigid proof or disproof of any statement. Finally, serious disease always tends to arouse superstition. The sufferer wants immediate relief from suffering and fear, and if science cannot promise this he turns eagerly to any one who promises to work a miracle on his behalf. The popularity of the numerous systems of healing, including faith healing is striking testimony of the strength of this impulse.

It is however a commonplace of science that an accurate observer working on a fallacious hypothesis may make valuable new discoveries. Although astrologers were devout believers in a complex system of absurdities yet they made

discoveries of considerable practical value and interest. Therefore medical science should always be ready to investigate claims that can be confirmed or disproved by observation, irrespective of the question as to the possibility of the truth of the theory which led to their discovery.

Rational therapeutics commenced only during the second half of the nineteenth century when the foundation of modern pharmacology was laid by the critical experimental analysis of the mode of action of drugs on the functions of the body. At the same time its development was influenced profoundly by the rise of the science of organic chemistry.

The first synthetic organic drugs introduced into medicine were the anæsthetics, these were followed by the antiseptics and in 1860 chloral hydrate was introduced. Since 1880 an ever increasing flood of synthetic organic drugs has been poured upon the medical profession and to-day their number is a serious embarrassment. The production of a new compound and the elaboration of methods for producing it on a commercial scale are expensive processes and the manufacturer recoups this initial expense partly by protecting his process by a patent and partly by introducing the new drug under a proprietary name. But if the drug is really useful alternative methods of manufacture are soon discovered which evade the patent restrictions and soon the new compound is advertised under a number of other fanciful names as well. Alternatively a series of new compounds with almost similar actions are introduced, each with a slightly differing chemical constitution, and all advertised, under different trade names—as for example the barbiturates. If the drug has been proved to be really useful it may be included in the pharmacopœia with an official name, but all the same the sale of the same remedy under other names continues. Then there are the preparations of endocrines for many of which extravagant claims are made which cannot be substantiated.

The outstanding and the pioneering work in chemotherapy is that of Ehrlich who introduced salvarsan, which has been a wonderful blessing to humanity. In his series, there were about 914 or more compounds and some of those that he discarded in

his experiments are being reintroduced to-day for various other purposes, for example, stovarsol, carbarsone etc. Since the days of Ehrlich considerable advances have taken place in chemotherapy. In addition the science of biochemistry has advanced to such an extent that to-day we have almost pure preparations of hormones which are coming more and more into their own in the treatment of various deficiency diseases. The knowledge of the action of vitamins and their importance in the physiology of the human body has led to the study of their chemistry and to-day a number of these can be synthesised in the chemical laboratory and therefore can be made cheaper and hence more easily accessible to the majority of sufferers.

The science of chemotherapy received a great fillip in the research into the treatment of sleeping sickness in the Congo for which atoxyl was first used. From the study of its chemistry and actions new derivatives were made by Ehrlich which were of great use in the treatment of syphilis.

Other directions in which chemotherapeutic activity led were in the synthesis of hypnotics, the local anæsthetics, and antiseptics in the treatment of bacterial infections.

One of the most fascinating subjects is the study of the relationship of chemical constitution to the pharmacological action of drugs; how a slight change in the side chain of a ring compound or the substitution of one radicle for another modifies the action in the human body, and how a slight change might increase or decrease the toxicity of a drug.

Many examples may be given to illustrate this. The discoveries of the exact chemical structure of adrenaline led to the synthesis of a large number of similar compounds which have an adrenaline-like action, e.g. synephrine, benzedrein, veritol etc. Taking the aromatic coal tar antiseptics, we find that the parent substance C_6H_6 has a low toxicity as it does not readily react with protoplasm. This capacity is given to it by replacing part of the H atoms by other groups, especially by OH forming phenols, or by COOH forming acids or by both. The OH radicle is the most active, the antiseptic and toxic action increasing with the number of OH groups, i.e. progressively from phenol, C_6H_5OH, to resorcin, $C_6H_4(OH)_2$ and Pyragallol, $C_6H_3(OH)_3$ but it is also influenced by the position of the OH groups in the ring, as for example, phluroglucinol, the isomer of pyragollol is not active. The introduction of the COOH group, i.e. benzoic acid does not render the substance very active, but the introduction of both OH and COOH groups as in the case of salicylic acid results in a compound less toxic, less antiseptic but having peculiar anti-rheumatic properties. NO_2 also develops the antiseptic property but adds its own toxicity also. The substitution of H by Alkyl groups as for example $C_6H_4O(HCH_3)$ forms cresols which are more powerful antiseptics and less toxic. Resorcin which is a dihydroxy benzol is an antiseptic but the action is increased if alkyl groups are substituted, the action increasing with the higher homologous alkyl radicles, the hexyl resorcinol being the most active. Such examples may be multiplied: by including an acetic acid group into aniline which is $C_6H_5NH_2$ we get the antipyretics; and if an ethyl group is also included we get even a better antipyretic, phenacetin. The addition or substitution of any ethyl group always gives a sedative effect. Taking sulphonal, which contains two methyl groups, the substitution of these by ethyl groups increases the hypnotic action. Then we have the relation of optic isomerism to pharmacological action. The naturally occurring hyoscyamine is mostly laevo and this is more active than the dextro.

These facts form the basis for the whole science of chemotherapy. We shall now take up a few of the important chemotherapeutic agents.

Take the drugs used in syphilis, the synthesis of these dates back to the examination by Ehrlich of the first aromatic compound of arsenic to be produced. This was atoxyl or Soamin. This is produced by introducing arsenic acid into the aniline ring, when arsanilic acid or para amino phenyl arsonic acid is produced. The term 'atoxyl' is a misnomer because this drug proved to be very toxic. Since the toxicity of atoxyl to the optic nerve was known the reason for this has been discovered to be the position of the NH_2 group in the ring in the para position. And whenever such a drug is produced there is bound to be more or less tropism for the optic nerve. Two other drugs

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Laboratory diagnosis of Typhoid fever and Interpretation of the Widal reaction

BY

(DR. V. IRAVATHAM.)

THE laboratory diagnosis of typhoid fever rests on two factors:—(i) Isolation of the organism from the body of patient and its identification (Bacteriological diagnosis), (ii) Serological changes, produced as a result of the infection with Eberthella typhi (Serological diagnosis).

Isolation of Eberthella typhi (B. Typhosus).

The organism is usually isolated from the blood, fæces and urine.

Some points about the cultural examination of the blood, stool and urine.

Blood culture.—The possibility of a successful recovery of the organism from the blood depends upon the period of the disease in which the examination is done. The most favourable time is the early phase of the infection i.e. at the stage of bacterimia which is usually marked during the first five days. The chances of success diminish rapidly after the first week.

For a successful result the following methods should be followed.—Five to ten cubic centimetres of blood should be withdrawn aseptically from a vein and transferred immediately under sterile precautions to a flask containing fresh sterilised ox-bile.

If the patient stays at a distance from the laboratory, transport may be facilitated by drawing the blood in a special Behring's venule, containing either sterile citrated saline or ox-bile or glucose broth.

Stool culture.—The chance of success in obtaining a positive result from the stool examination are shown in the table :—

First week	...	... 15 per cent. positive.
Second week	...	... 65 „ „ „
Third week	...	... 85 „ „ „

Isolation of E. Typhi from the stool is a very important step in the practical diagnosis of typhoid fever.

Urine culture.—The elimination of the organism in the urine is more transient and is of shorter duration (Transient baciluria).

Collection of material

Blood.—This is usually taken from the superficial veins. Strict asepsis should be observed.

Fæces.—The most important factor is the freshness of the stool. Failure to remember this often ends in negative results and is the source of much misunderstanding between the physician and the bacteriologist.

Urine.—Catheter specimen should always be preferred. In the cases of male, however, the mid-stream urine may be taken.

Serum diagnosis.—In the early days of the disease, it is not possible to demonstrate the presence of agglutinins in the blood stream. But after the first week, appreciable amounts appear in the blood and the titre limit gradually increases until it reaches its maximum on the twenty-first day.

Hence the best period in which positive diagnosis can be obtained from Widal reaction is after the first week of the disease.

First week	...	... 3 per cent. positive.
Second week	...	... 75 „ „ „
Third week	...	... 90 „ „ „
Fourth week	...	... 95 „ „ „

With the technique and the reagents standardised, one must have some idea of what is the normal titre. In a place like Madras where enteric infections are endemic, several persons are likely to have received subclinical doses of infection from time to time. A titre of 1 in 25 for the O and 1 in 50 for the H therefore, should not be considered diagnostic of infection. Several normal areas in Madras give a titre of 1 in 25 for O probably because the O antigen is more universally distributed among the intestinal pathogens.

Since antibodies take sometime for development, time is an important factor in assessing the agglutinin titre of the serum. We must therefore know on what day of the illness the blood is examined. Thus a titre of 1 in 50 though without significance in the third week of the disease, cannot be overlooked if obtained within eight days of the onset. In such a case, a repetition of the test is warranted, and a definite rise over the previous titre alone points towards infection. As a broad working rule a titre of 1 in 50 for the O and 1 in 100 for the H anytime during the second week of illness should be suggestive of infection.

The question is sometimes asked, " What strength of agglutination titre is diagnostic or suggestive of infection ? "

The answer is clear and definite : No arbitrary titre can be selected which is positive in the diagnostic sense or below which it can be regarded as diagnostically negative. An agglutination reaction is simply one item of evidence to be considered in relation to all other evidence available.

Certain general principles may be laid down, however, to govern the clinical utilisation of this procedure :

1. Given a patient presenting symptoms suggestive of enteric fever—which, it must be remembered, includes infection with any of the organisms in the Salmonella group (of which, there are about twelve species capable of causing continuous fever) a negative reaction to the suspensions used may signify that : (*a*) the patient does not have enteric fever ; (*b*) that the specimen was taken before agglutination appeared ; (*c*) that the disease is of the unusual type and caused by an organism

not represented in the suspensions used. The first two alternatives are differentiated by a repetition of the test; the last by a resort to attempts to isolate the organisms by culture.

2. A negative reaction in the second or third week of the disease is of definite negative diagnostic value and repeated negative reactions render the clinical diagnosis unlikely.

3. A positive reaction must be considered in relation to:—

(*a*) the distribution of the agglutinins in the normal population,

(*b*) the stage of the disease at which the test is made, and

(*c*) the history as regards vaccination.

4. As is usually the case with many laboratory procedures the trend of a series is of greater value and significance than a single determination.

5. Quantitative reactions are far more clinically valuable than tests with one or two arbitrarily selected serum dilutions.

To conclude the bacteriological diagnosis of typhoid fever may be summed up as follows:—

of the disease.

First 7 to 10 days	...	By blood culture.
After the tenth day	...	By Widal reaction.
At all stages but particularly after the second week	...	By stool and urine culture and Widal reaction. The diagnostic value depends on a rising titre.

Banana and Banana Powder Therapy in Diarrhœal Diseases of Infants and Young Children

(*The Practitioner, Dec. 1938*)

AFTER treating fifty-six cases of acute diarrhœal disorder at the Children's Hospital, Philadelphia, with banana powder or pulp, Brubaker came to the conclusion that this method of treatment was more effective than conservative measures. Other authors have also extolled this form of therapy, as it prevents loss of weight and causes an immediate and noticeable reduction in the number of stools. The general method of the treatment is described by E. A. Socola (New Orleans Medical and Surgical Journal, October, 1938, 91, 192). Fully ripe bananas, creamed by the Manning-Bowman creamer, banana powder (Melotose No. 1) manufactured by the Food Concentrates, Incorporated, and boiled water were the materials used. For children under thirty pounds the minimum amount was one-third of a banana or one level teaspoonful of banana powder per pound of body-weight in twenty-four hours. When ripe banana was administered sufficient water was given with the fruit or separately to maintain the daily fluid quota. Brubaker divided the total calculated daily banana ration into single feedings every two hours during the day and double feedings at 10 p.m. and 2 a.m. The author has used the method of dividing the total twenty-four hour banana ration into ten single feedings, i.e. at 6 a.m., 8 a.m., 10 a.m., 12 noon, 2 p.m., 4 p.m., 6 p.m., 8 p.m., 10 p.m., and 2 a.m. After forty-eight hours of exclusive banana or banana powder and water feeding the child was placed on a transition diet consisting of skimmed cow's milk or skimmed lactic-acid milk with banana or banana powder. In the milder cases and in older infants and children other articles of diet were included during the second forty-eight hours, such as strained beef-broth, well-cooked cereals, dry toast or crackers, but in cases of infectious diarrhœa or bacillary dysentery the transition diet consisted of skimmed lactic-acid milk and banana or banana powder, and was given over the period of forty-eight hours according to clinical results. Breast-fed infants

were withdrawn from feeding at the breast for forty-eight hours, after which time it was resumed, care being taken during that time to preserve the supply of breast milk by artificial stimulation.

Severe Dermatitis Due to Sulphanilamide

(*Clinical Journal, Feb. 1938*)

DERMATITIS is one of the toxic effects of sulphanilamide. J. O. Finney reports a case in which it was so severe as to require admission to hospital. A man, aged 29, came under observation. Two weeks before, a practitioner prescribed four tablets of sulphanilamide four times daily for acute recurrence of old gonorrhœal prostatitis. About the sixth day of treatment the patient suffered from itching of the skin of the face, arms and chest. This became more severe, and on the last day of treatment he noticed a rash over his face, arms and chest. During the two days previous to admission swelling of the face and arms occurred, and the rash became marked on the back, buttocks and dorsum of the feet.

On examination the temperature was 101·8°, the pulse 120, the respiration-rate 20 and the blood-pressure 130 systolic, 80 diastolic. He rubbed various areas of his skin frequently, and complained bitterly of general itching and of "tightness" of his face. There was a symmetrical maculo-papular rash over the body, most marked on the face, anterior surface of the chest, flexor surface of the arms and extensor surface of the fingers. A similar though less severe reaction was present over the buttocks, posterior part of the thighs and the dorsum of the feet. The lesions were in some areas discrete while in others they were confluent, so as to form large patches. There was œdema of the face, which all but closed the eyelids; over the chin there was oozing with crusting. The fingers were so swollen that he could not make a "tight fist". He was put to bed and was much relieved by oatmeal baths. The eruption gradually disappeared in 5 days.

[Administration of Vitamin C—Cantan and Redoxon—relieves its toxic manifestation. *Editor.*]

Sulphanilamide in Actinomycosis

(*Clinical Journal, Nov. 1938*)

O. Walker reports the case of a soldier, aged 23, admitted to the Queen Alexandra Military Hospital, Millbank, in September, 1937, with a gangrenous appendix. A discharging sinus followed and was explored but failed to close. On February 1, 1938, actinomyces were demonstrated in the pus and mass filling the right iliac fossa was palpable. Potassium iodide and Lugol's iodine were given without benefit. On March 3 the discharge was as profuse as ever and "sulphur granules" showing microscopically typical filaments of actinomycosis were demonstrable. A gramme of sulphanilamide was given thrice daily by mouth for a week, beginning March 4. Diminution of the discharge and disappearance of the granules rapidly followed. On March 20 the treatment was resumed for 5 days. On March 29 there had been no discharge for 4 days and the sinus had closed. When seen on May 12 the wound was firmly healed and the mass in the iliac fossa had disappeared.

Severe Burns Due to Celluloid Combs

HOWARD Fox (Journal of American Med. Association, 1937, ii, 1938; clinical journal, March 1938) calls attention to severe burns from ignition of celluloid combs usually used while the so-called "water wave" of the hair is being carried. He reports six cases of severe burn due to warming of the head.

[Such a danger is more likely in India where the baneful habit of wearing celluloid bangles has become very common and to prevent such accidents their use must be condemned.

The Editor.]

Treatment of Tetanus by Intravenous Injection of Alcohol

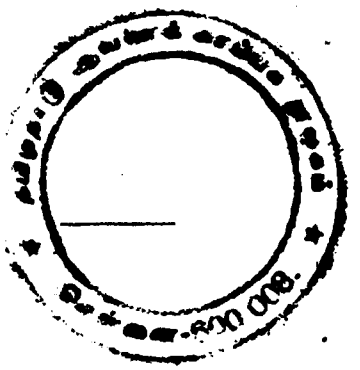
(*Clinical Journal, April 1938*)

MERLE, Francois and Jouve refer to the tetanus treatment introduced by Dufour, which consists of combining serotherapy with anæsthetizing the patient by administration of chloroform or ether. Grisolle, in his book, quotes the statistics of Prevost, who obtained 22 recoveries under this method in 34 cases of tetanus, adding that no other method of treatment gives such a good figure. The explanation is that chloroform liberates the tetanus toxin from the spinal cord. *In vitro* this has been done by means of ether or alcohol, and it appears that chloroform acts similarly *in vivo*. But there have been numerous failures of this treatment. Moreover, many of the subjects of tetanus are aged or alcoholic and have defective kidneys, and there is danger of producing hepatitis by repeated chloroforming. A long experience of treating chronic pulmonary suppuration by intravenous injection of alcohol has shown the present authors its safety, and they thought that alcohol would have a greater action on the nerve centres than the small quantity of chloroform which would penetrate during anæsthesia.

They have treated tetanus by daily injections of 20,000 units of antitoxin, almost exclusively by the subcutaneous or intramuscular route, combined with intravenous injections of 10 to 40 c. c. of a 1 in 3 solution of absolute alcohol in 30 per cent glucose. They prefer the glucose solution to normal saline as less sclerozing. The wounds were cleansed as completely as possible, but under chloroform only in case of necessity. The injections never gave rise to the slightest complication. Ten cases were treated by this method, and complete recovery took place in 7. Three of the cases were fatal, but in none was death due to the action of the tetanus toxin on the nerve centres. Thus a man, aged 35, sustained a wound of the forearm which was soiled with earth. Symptoms

began 7 days later. Three days after the onset of trismus he was brought to hospital suffering from severe general tetanus. The wound was cauterized under choloroform. Daily subcutaneous and intramuscular injections of 20,000 units of antitoxin and an intravenous injection of 30 c. c. of the alcohol solution were given. The spasms diminished after 10 days, and after 15 days disappeared, but a large abscess formed in the buttock and the patient died from the cachexia without any recurrence of the spasms. In the two other fatal cases death was due to pulmonary complications.

The following is a successful case: On September 21, 1937, a youth aged 19, wounded his left thenar eminence in manipulating a cask. Trismus began 4 days later and the spasms extended to the back and limbs. On Sept. 26th he was admitted to hospital with generalised tetanus, intense trismus and a temperature of 103·2°. The wound appeared to be healed; it was, however, opened up and cleansed. From a fragment of tissue in its depth the tetanus bacillus was cultivated. 20,000 units of antitoxin and 20 c. c. of the alcohol solution were injected daily. Ten days after beginning the treatment improvement was marked and recovery followed.



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The Trichinopoly District Medical Association

A MONTHLY meeting of the above Association was held at 5 p. m. on Sunday the 26th March, when Dr. K. C. Paul, M. D., Diabetes Specialist and honorary Physician, Government hospital, Royapuram, Madras, delivered an interesting lecture on "Diabetes". Dr. N. R. Srinivasan was 'At Home' and Lt. Col. N. K. Bal, M. C., I. M. S., presided. About 40 doctors were present.

In the course of his lecture Dr. Paul said that "Diabetes was as common in the female as in the male and cases were seen in infants also the youngest being a child of 8 months old. But the usual age incidence was between 35 and 50 the most useful part of individual's life. The majority of cases were amongst middle class people.

A good proportion of diabetics were amongst medical men themselves. It was a familial disease and was known in ancient India also. It was a hereditary disease though a generation or two might miss it. There may be a few diabetics without any signs or symptoms but the majority of cases are characterised by the three pollies, chief amongst the causes was anxiety, neurosis, injury and septic conditions in the body especially, pyorrhœa, alveolaris and intestinal intoxication accompanied by over-eating and sedentary habits. Though insulin is a specific in the treatment of diabetes, it is of especial use in emergencies such as acute-diabetes, carbuncle and coma and many a life has been saved by this drug. Most diabetics could avoid the daily intake of insulin by adjusting their diet according to their needs and sugar toleration. Regulated exercise and a day's fast once a week or at least on the Ekadasi day once a fortnight was a useful adjunct." An interesting discussion followed in which many members took part.

With a few remarks by Lt. Col. N. K. Bal and a vote of thanks by the secretary to the lecturer, host and the president the meeting terminated at a late hour.

P. A. S. RAGHAVAN,
Secretary.

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which are similar and which are used in medicine are Tryparsamide and carbarsone. We are warned to examine the ocular fundus before instituting treatment with tryparsamide and to keep a watch on the eye during treatment. With carbarsone, eye injury is a possibility, but perhaps owing to the method of administration which is oral, and lack of statistics of numerous cases so treated such an occurrence has not been noticed in literature.

Ehrlich found that atoxyl which was a pentavalent organic compound of arsenic was very active against sleeping sickness but had little effect on the parasite outside the body. He concluded that in the body atoxyl was reduced to the trivalent form and so started experimenting with trivalent compounds. Bertheim produced salvarsan as the 606th in his series and this drug was studied by Ehrlich and Hata who found its efficacy in syphilis. Later owing to the acidity of its solution and the need for alkalinising it and other disadvantages, 914 or neosalvarsan was produced. This had a slightly different constitution and had a longer side chain on one of the two rings. This could be easily given intravenously and is the most popular drug in the treatment of syphilis today. But it has its disadvantages. The drug in solution is easily decomposed and bulk solutions cannot be made. The slightest agitation during solution causes decomposition. It has the other toxic manifestations of salvarsan, as well Sulpharsphenamine or Sulpharsenol is a little different from neoarsphenamine in having a double side chain and an extra atom of oxygen in each side chain. It was thought that this would be less toxic. Though it is less irritant and can be given intramuscularly or even subcutaneously the incidence of dermatitis has been greatest with this drug. The action is said to be due to injury of the tiny vessels of the skin by the arsenic. When combined with heavy metals salvarsan had a more powerful action and so drugs like silver salvarsan were produced. Bismarsen has less bismuth and arsenic than would be given by introducing Bi and As separately and so is not popular. When Ehrlich first introduced salvarsan he had a very simple theory of its action that certain side chains in the drug combined with certain side chains in the parasite and caused death of the parasite. But we know that this is not the case. The modern theory is that

salvarsan has no direct parasiticidal effect but is converted into an active form an arsenoxide in the body which is highly parasiticidal. This arsenoxide can be produced outside the body but was found to be too toxic for ordinary use.

Next, let us take the chemotherapy of Malaria. Quinine still holds its own in the treatment of this disease. By reason of the millions involved, quinine is likely to continue as the mainstay of the treatment of malaria for a long time to come. But I was greatly amused by the propaganda done by the Quina Bureau against the chemotherapeutic agents and the counter propaganda by Bayers. This seemed to be in extremely bad taste as the world cannot do without quinine for some considerable time longer and the utility of the newer remedies has been proved beyond doubt. As for the use of quinine in malaria, the Malaria Commission of League of Nations in their latest report recommends a mean daily dose of 1 g. of quinine hydrochlor for from 5 to 7 days. With such treatment the trophozoites disappear on an average on the third day and do not appear until after a latent period of varying length in the course of the primary relapse. The relapse rate in primary cases is as high as 50%. Quinine probably acts by slowing the asexual reproduction and killing a few parasites which act as antigens and stimulate the production of antibodies. The action is more marked when the body has already acquired a certain amount of natural immunity and so the treatment of relapses is more satisfactory than the treatment of primary cases. In clinical prophylaxis opinions differ greatly in regard to the value of quinine. The Malaria Commission of the League points out that very useful results can be obtained with daily doses of quinine of 0·4 gm. (about 4 grs.) given during the whole of the malaria transmission season and even for a few weeks longer.

The chief advantage of quinine is however that it requires no such close supervision as is necessary in the case of atebrin nor is it so likely to cause toxic reactions in children, among whom gametocyte carriers are more numerous than among adults living in the same environmental conditions.

During the war, shortage of quinine led to various experiments in Germany. Starting with methylene blue which had

been shown to have some effect in malaria, plasmoquin was arrived at. Though originally derived from methylene blue the constitutional formula of plasmoquin has some analogies to that of quinine. Plasmoquin is a toxic compound and by itself it has no advantages in the treatment of any acute attack of any form of malaria. The Malaria Commission of the League recommends a daily dose of 10 to 30 mg. (1/6 to 1/2 gr.) associated with atebrin or quinine given either simultaneously or after a certain lapse of time. Especially when given with atebrin toxic reaction may occur. Asthenia, cyanosis, vomiting and gastralgia have been noticed in about 50% of cases. The importance of plasmoquin lies in its ability to destroy the gametocytes of M. T. On B. T. and quartan it acts on the gametocytes of both and on the asexual varieties of the quartan, its most remarkable effect is on the gametocytes of M. T. Hence it should be of particular value in prophylaxis as it makes the gametocytes non-infective to mosquitoes. In doses of about 1/6 gr. a day or 1/3 gr. twice or thrice a week it does act as a prophylactic. But a higher dosage is necessary to make it a true causal prophylactic and this verges on the toxic.

Atebrin, a later product, is somewhat related to plasmoquin. The methoxyquinoline nucleus is replaced by amethoxyacridine nucleus. It is a yellow, fluorescent product. For injection atebrin dimethane sulphonate has been prepared under the name of atebrin musonate. It is very soluble whereas atebrin is soluble to the extent of 7% at 40°C. The peculiarity of atebrin is that while the action on the various types of malaria is similar to that of quinine it acts quicker and more effectively especially on the asexual types of M. T. 0·3 g. which should be the average daily dose of atebrin for an adult has a slightly more rapid action than quinine in doses of 1 g. The parasiticidal action also lasts longer. Atebrin thus has a more rapid action than quinine. The action on the gametocytes is similar to that of quinine. Injections remove the parasites even quicker than oral administration.

So far as clinical and mass prophylaxis are concerned there is evidence that bi-weekly doses of 0·2 g. or about 3 grains of atebrin given during the whole of the malaria transmission

season and even for a few weeks longer exert a definite action on the number of attacks.

Toxic symptoms are not frequent but have been reported. There may be gastro-intestinal symptoms and nervous symptoms like giddiness, delirium and even convulsions. The yellow coloration of the skin is harmless and tends to disappear. The question of the inocuousness of these synthetic remedies during pregnancy has not been fully established as yet. Dikshit has done some work on this problem and believes that a combination of quinine and plasmoquin is better in such cases. Atebrin has some effect on the uterine muscle in experimental animals but no case has been recorded where it has caused any untoward result in pregnancy.

One of the most fruitful fields for the experimental chemist and the manufacturing concerns has been the field of hypnotics. Insomnia is such a common symptom in these days of stress and competition and world unrest and its causes are so numerous that hypnotics of varied origin and very different chemical constitution are in great demand. The hypnotics can be broadly classified under two main heads: the analgesia hypnotics and the hypnotics that have no effect on pain. Morphine is the only member of the first group. Of course the other opium derivatives are included under this head. But anybody who has a great faith in morphine as a reliable hypnotic under all circumstances will very soon get disillusioned. A quarter of a grain will send most people to sleep, but in some cases there will be some hours of preliminary excitement which may be accompanied by distressing nausea. Sometimes even when it is given for pain, specially in women, the pain is relieved but there is little tendency for sleep to ensue, as the patient is in a condition of pleasant languor. Among the other kinds of hypnotics attention had been greatly rivetted on the barbiturates. This group is theoretically formed by combining urea with a malonic acid group. We then get malonyl urea or barbituric acid, where at the end of the chain there are two H atoms which can be replaced by simple alcohol or alkyl groups like C_2H_5 or aromatics groups like C_6H_5 or other more or less complex groups containing one of the homologous alkyl groups. These are divided again into two classes. One where the side

chain is small and which are not decomposed readily in the body and are therefore of more prolonged action; the other where the side chain is more complex. The more complex or the longer the side chain the quicker is the destruction and the more short-lived will be the action. To the first group belongs veronal and luminal, and to the second group belong, amytal, evipan, pentothal, Nembutol, Phanodorn, ortal etc. The sodium salts of these acids are soluble and may be given by injection producing instantaneous sleep. Another excursion in chemotherapy on these lines is the combination of some of these barbiturates with the coal-tar analgesics in order to produce some of the very popular analgesic tablets. The use of these compounds are familiar to you. About 60 barbiturates are known but theoretically it is possible to create at least 1225 such compounds.

It is true that such combinations act synergistic. Magnus found in rabbits that the stimulant action of amidopyrine was diminished by barbitone and that the depressant action of the latter was delayed and diminished by amidopyrine. The barbiturate in large doses tend to depress the sensory irritability to faradic current and smaller doses of the true analgesic are required to exert a pain killing effect. But there is some danger in the indiscriminate use of these by the laity, for though the dose of the barbiturates in these is small, repetition of such doses may sometimes lead to cumulation as amidopyrine has a short action and barbitone a prolonged action. Automatism is a phenomenon sometimes observed when patients are asked to take a dose of these barbiturates at night, when the patients can only remember that they were asked to take a dose but not if the dose had already been taken so that, cases have occurred when a whole bottle of tablets had been swallowed mechanically during the night. It is much more rational to prescribe the hypnotic and an analgesic separately. Examples of such proprietary mixtures are:

Allonal	...	amidopyrine	with allurate
Cibalgin	...	do.	with dial
Compral	...	do.	with trichlor ethyl urethane
Veramon	...	do.	with barbitone.

A number of other such combinations may be remembered by you.

Time is passing and I cannot touch, more than in passing reference to the brilliant researches in dye-stuffs as antiseptics or the introduction of protamine and zinc in insulin for slowing its action, or on the chemotherapy of leprosy, leishmania etc.

Lastly, I cannot but stress the extraordinary vista for the future of therapeutics which has been opened up by the introduction of the sulphonamide group of drugs, in the treatment of coccal and bacillary infections. Although the first azo dyes containing the sulphonamide group were isolated as long ago as 1908 they were only tested clinically in the years 1933 to 1935. In the latter year, a German worker, Domagk, found that the compound called prontosil was effective against a lethal dose of haemolytic streptococci injected into the peritoneum of the mouse. Intensive study of this and allied substances, both in animals and in man, quickly followed. Chemists, experimental pathologists, and clinicians all took part, and a flood of communications on this subject rapidly appeared. Already these compounds have made good in many forms of highly pathogenic coccal infections, such as erysipelas, puerperal fever, pneumococcal, gonococcal and meningococcal diseases, and also in certain coliform diseases. The field is as yet not fully explored, but we may even now confidently affirm that the early promise of success of these new drugs is more than justified. The effective blood content of the active substances is being ascertained and the indications and contraindications are becoming more widely known. Since the brilliant work of Ehrlich and his pupils more than 30 years ago there has been no chapter in chemotherapy to equal this. The rapidity with which this new chemotherapeutic measure has become an established practice and the degree of control that is possible, illustrate in striking fashion the power of modern medicine to add effectively and rapidly to the physician's armamentarium.

Domagk (1935) stated that the administration of about 1/10 to 1/50th tolerated dose of prontosil for three to five days after infection protected most of the mice which were inoculated with Haemolotic streptococci. Later it was found that the

Prontosil was converted into sulphanilamide in the body and that it was this that was mostly responsible for the action.

A number of these derivatives are used in medicine now. The chief are :—

1. Prontosil, an azo dye, insoluble in water. This has two benzene rings united by an azo linking. This has to be given by mouth.

2. Prontosil soluble is more complicated in its chemical formula and has in addition a naphthaleine ring. It can be given in 5 per cent solution intramuscularly or intravenously.

Rubiazol is a French preparation very similar to prontosil but has a COOH group in addition.

Sulphanilamide is simpler and is p-aminobenzene sulphonamide. It has a NH_2 group at one pole i.e. the para position of the benzene ring and a $SO_2 NH_2$ group at the other pole. It has unfortunately at least 22 synonyms by which it is known in various countries. It is a white crystalline powder with a bitter taste and no odour, soluble to the extent of 0·80 per cent at room temperature. The best method of preparing a solution for injection is to dissolve at 80°C. 1 g. of the drug in 80 c.c. of dist. water containing 0·5 per cent NaCl—After sterilisation in the autoclave at 115 to 116°C. for 30 minutes the solution is allowed to cool to body temperature before injection. Below body temp. this will crystallise out. Other compounds are,—

Proseptasine, a benzylamine benzene sulphonamide and Soluseptasine put up in 10 per cent solution.

Uleron or Diseptal insoluble and is used in tablets of 0·5 g.

M and B 693 or P-aminobenzene sulphonamine pyridine or Dagenan, is also not soluble.

Sulphanilamide is rapidly absorbed from the gut, the process being complete in 3 to 4 hours. Subcutaneous injection does not produce a quicker rise in blood concentration. The peak in blood is reached in about 3 hours and gradually diminishes to nothing in 24 hours. This prolonged retention is important; other chemotherapeutic dyes are excreted too readily. Persistence in the blood is due to reabsorption in the renal tubules.

Impaired kidney function will cause a delayed excretion. Diuresis will increase the excretion.

That the protective action is due to the formation of sulphanilamide is shown by the fact that, if the molecular equivalent of 6 mg. of sulphanilamide in terms of prontosil soluble, 20 g. is injected into mice, the blood levels of free sulphanilamide at the end of 4 hours are essentially those obtained by the same period after the injection of 6 mg. of sulphanilamide. The drug is excreted into all the body fluids. It is found in the menstrual blood and may pass to the foetus during pregnancy and so one should be cautious in giving the drug in pregnancy as we don't know the action on the foetus. It is also found in milk. Of special interest is the passage of the drug into the cerebro-spinalfluid. Sulphanilamide passes more readily than prontosil. The excretion is either as unchanged sulphanilamide or partly as an acetylated compound. The urine is rendered alkaline because of the lack of reabsorption of bicarbonates.

In modern therapy the estimation of sulphanilamide in the blood is important but it requires some chemical experience. 1 c.c. of blood is diluted with 2 c.c. of dist. water; 1 c.c. of 20 per cent aqueous solution of trichloracetic acid is added and filtered. To 1 c.c. of filtrate is added 1 c.c. of 0·5 per cent sodium nitrate solution. After 3 minutes 0·5 c.c. of a 1 per cent alcoholic solution of dimothyl-a-naphthylamine is added and the whole mixed. After 15 minutes the colour is compared with a standard.

Experimental investigations have shown that sulphanilamide has a particular prediction to haemolytic streptococci and has only a slight effect on other streptococci, like S. viridans. It has no action on S. faecalis. In man sulphanilamide has been tried in numerous strepeococcal infections with varying effects. In puerperal fever the evidence suggests that despite the variability in the severity of the fever the sudden drop in mortality must of necessity be correlated with the administration of these drugs. As a prophylatic it may be given to such cases as run a risk of developing sepsis. About 3 g. per day may be given beginning from the third stage of labour for a week.

In Streptococcal Pyelitis infected with haemolytic streptococci sulphanilamide clears up the infection. S. faecalis is resistant

but quickly yields to mandelic acid. B. Coli infections are also amenable. In erysipelas sulphanilamide was found specific, 6 g. being given per day, till apparent cure and thereafter 3 g. daily for about a fortnight. In tonsillitis the same good results have been obtained.

In pneumonia sulphanilamide is particularly of value in the streptococcal infections and in type III which is virtually a streptococcus. M & B 693 is of particular value in all types of pneumococcus infection. Uleron is similar to sulphanilamide in this respect. M & B 693 differs from sulphanilamide in that one H atom of the S02NH2 group is replaced by a basic pyridine group. It is definitely pneumococcocidal and a definite action on the capsules has been seen. The capsule becomes swollen, crenated and eventually disappears. The action on pneumococci can take place even in the absence of leucocytes but a better action is seen in the presence of healthy leucocytes and in the presence of immune serum. Most remarkable cures have been reported in most serious types of pneumonia.

M & B 693 is also equally effective against meningococcus and the gonococcus.

In meningococcic infections both sulphanilamide and M & B 693 are of equal value. It may be given by mouth and also by injection. M & B is not easily given by injection. But sulphanilamide may be given subcutaneously and intrathecally in 0·8 per cent solution. The amount injected into the spinal canal varies from 5 to 30 c.c. according to the amount of cerebro-spinal fluid withdrawn. It has not been definitely decided which of the sulphanilamide group of drugs is of the greatest use in meningococal meningitis. Soluseptasine and proseptasine have also been reported to have saved life in such cases. There is some evidence that in order to prevent relapses these drugs should be continued for sometime after the disappearance of clinical symptoms.

In Gonococcal infections. The action of sulphanilamide in this infection is explained by its excretion in sufficient concentration in an alkaline urine. Unfortunately there is no indication here of the best drug to use and the method of use. Some workers believe that the best results with sulphanilamide

is obtained only after some amount of natural immunity has been established and so delay administration until 8 to 10 days after the beginning of symptoms. Others emphasise the need to begin treatment at once. Most people agree that local measures are equally important. In addition to sulphanilamide and prontosil soluble proseptasine and soluseptasine have also been used. Proseptasine seems to be very inferior in the treatment of the disease in the male. Soluseptasine in daily doses of 5 g. for about a fortnight or more produced some good results. Of special interest is uleron. This has been largely employed in Germany where it is considered superior to other drugs. In Britain opinion is divided. Very acute cases do not respond immediately to uleron; but when treatment is deferred for a few weeks, say for 3 weeks, treatment at once was followed by prompt disappearance of symptoms. It is suggested that the body tissues must become somewhat resistant to the infection before uleron produces its best results. This also explains why it has a better effect in the females, who as a rule come for treatment at a later stage of the disease. Uleron is of no prophylactic value in gonorrhœa. M & B 693 has now been widely tried and it seems to have even a better effect. There is a tendency to prefer M & B 693 in gonorrhœa in Britain. But in Germany, uleron is preferred. Sulphanilamide started a week-after injection is as efficacious.

In other infections, which are quite varied in nature these drugs have been employed. Soft sore is quickly cured. Staphylococcal infections are also cleared. It has been tried in malta fever also with success.

As for dosage it is now recognised that these drugs must be given like digitalis, by rapidly attaining and maintaining a certain concentration of the drug. Thus an initial dose of 3 to 5 g. is suggested, while if four hours later the concentration in blood is below 10 mg. per 100 c.c. subcutaneous injections are advocated. The majority of people prefer oral administration with intramuscular injection of the soluble products. The total daily dosage of sulphanilamide is suggested a 1 g. for every 20 lb. body weight with a maximum of about 5 g. In children proportionately higher doses are needed. Prontosil soluble is

best injected intramuscularly. It is risky intravenously. Mixed with glycerine up to 20% it has been used as a gargle and for painting mucous surfaces. Sulphanilamide has also been used as an ointment.

Toxic Reactions: As with every other chemotherapeutic remedy a number of toxic reactions have been ascribed to the administration of the sulphanilamide group of drugs. Fortunately most of the reactions described have been mild and apart from the staining of the tissues with prontosil have consisted of cyanosis, nausea, vomiting, headache, palpitation, dizziness and epistaxis. The cause of the majority of these reactions is as yet unknown. Sulphaemoglobinaemia, it is suggested, is due to the ingestion or liberation in the gut of sulphur. Other symptoms suggest a hyper-sensitivity on the part of certain individuals. Unfortunately, at present there is no possibility of anticipating such idiosyncrasy. The reactions associated with this group are classified as follows:—

1. Reactions affecting the central nervous System.

2. Reactions affecting the skin: rashes sometimes associated with exposure to light; exfoliative dermatitis.

3. Reactions affecting the haemopoietic system: Leucopaenia, agranulocytosis, acute haemolytic anaemia, thrombocytopaenia. Up to the present about 15 cases of agranulocytosis have been reported and from the great number of people so far treated this is a small number indeed. In all these patients the dosage was fairly high and was continued for a number of weeks. It is better to stop treatment after a fortnight and repeat if necessary.

Acute haemolytic anaemia occurs much earlier usually between the third and seventh days. Fortunately this also is very rare. Cyanosis is due among other causes to the occurrence of methaemoglobinaemia and sulphaemoglobinaemia. Any drug which has the group C6H5N—is capable of producing methaemoglobinaemia. When compounds such as aniline, acetanilide, sulphanilamide enter the blood the aminogroup is oxidised to hydroxylamine. When no sulphur is present in the blood this is reduced by the Hb and converted into methaemoglobin. In

the presence of sulphur, sulphaemoglobin is formed. When there is excessive formation of H2S or the presence of a suitable catalyst causes the sulphide to combine thus with Hb. To avoid an excess of sulphides all sulphur-containing food should be excluded, a low residue diet should be given, and all purgatives except liquid paraffin should be barred, for at least three days before giving the drug. A single injection of 1 mg per kilo of methylene blue produces a great reduction in cyanosis in methaemoglobinaemia. In severe cases transfusion may be needed.

The mode of action is still a subject of much study and speculation and I do not propose to take up your time in discussing this. But it may be stated that while prontosil is without action outside the body, in vivo it is actively bactericidal. Sulphanilamide also is without effect outside the body, but in blood and in culture media it exerts a lethal action on the bacterium. The blood may also become bactericidal within an hour of administration or after a delay of a day or two. A lag phenomenon is often noticed; i. e. during the first day of giving the drug multiplication of bacteria may continue though with diminished vigour. It is suggested by Whitby that sulphanilamide interferes with the metabolism of the bacterium, perhaps by removing something from the nutrient medium or the blood which is necessary for the ordinary survival and growth of the organism—while immune therapy is certainly a great aid in the cure in some cases of particularly susceptible organism like pneumococci, M&B 693 may act by itself without the intervention of immune processes or the phagocytic influence of the leucocytes. It has been found that administration of these drugs confer an immunity on the subject which is quantitatively similar to that obtained with the aid of sera or active immunisation. Much more remains to be done before we are clear about the mode of action of these potent drugs of the sulphanilamide group, the information of which marks one of the most momentous advances in our time in therapeutics.

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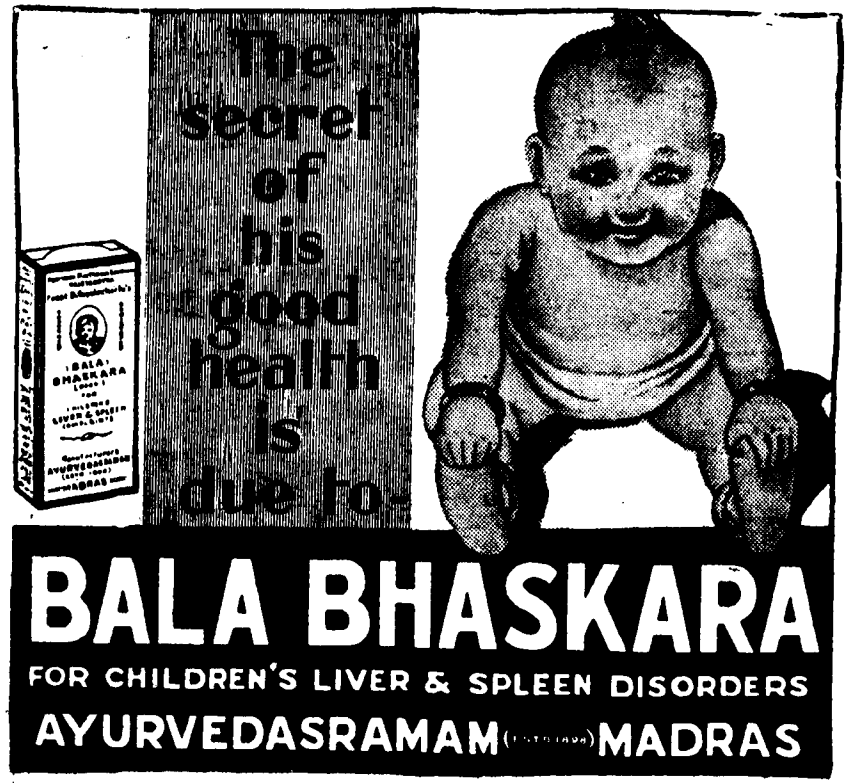

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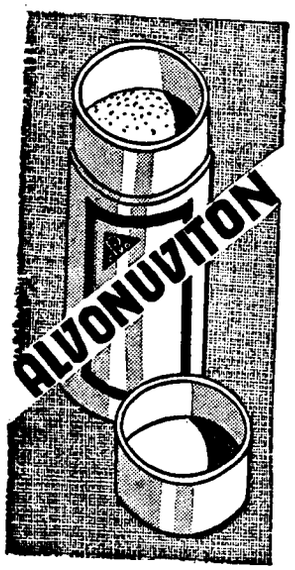

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