deficiencies are rather rare. It has been suggested that these vitamin deficiencies constitute a primary aetiological factor in the sprue syndrome (Verzar and McDougall, 1936; Castle, Rhoads, Lawson, and Payne, 1935). There is no satisfactory evidence of a direct relation between these vitamins and the fat-absorption mechanism (Frazer, 1947b). The signs of these deficiencies can be dramatically relieved without any effect on the fat-absorption defect (Cooke *et al.*, 1946). Classical cases of deficiency of these vitamins may occur with normal fat absorption. These deficiencies, which come and go during the course of the sprue syndrome, are probably secondary changes attributable to successful competition with the host for common essential nutrients on the part of intestinal bacteria.

Conclusions

It is concluded that the underlying fat-absorption fault is a defect in particulate absorption. The consequent absorption and excretion of fatty acids account for most of the major features of the sprue syndrome. Certain intermittent characteristics may be attributed to high growth of intestinal bacteria. The primary cause of faulty particulate absorption probably varies in different cases—many cases of tropical sprue may be primarily due to dietary faults, whereas some underlying defect, possibly an enzyme deficiency, may be a major factor in most cases of non-tropical sprue and the coeliac syndrome. Intestinal flora changes occur secondarily in most cases of sprue, but they may have a more important aetiological role in some cases of gastro-colic fistula. The final picture of the aetiology of the sprue syndrome will be achieved only as a result of further detailed study of the fat-absorption defect and experimental investigations designed to differentiate primary and secondary changes.

Much of the original work referred to in this paper is still in progress as part of the programme being undertaken in the Department of Pharmacology, University of Birmingham, by a team which includes Dr. J. M. French, Dr. M. D. Thompson, Dr. H. G. Sammons, Dr. R. Schneider, Dr. P. E. Sagrott, Mr. W. R. Pover, Mr. W. D. Brown, Mr. G. A. Rowe, and Mr. B. G. Taylor. While acknowledgments are made in the text to individual members with regard to points with which they have been especially concerned, the progress of the work is essentially dependent upon the combined efforts of the whole team. I am most grateful to many colleagues on the staff of the Birmingham United Hospital, especially to Professor T. L. Hardy, Dr. W. T. Cooke, Dr. A. L. Peeney, Dr. C. F. Hawkins, and Dr. Garfield Thomas, whose close collaboration and help have been invaluable. I am indebted to the Medical Research Council and the Sir Halley Stewart Trust for financial assistance in this work.

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THE TREATMENT OF MALIGNANT TERTIAN MALARIA*

BY

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The early diagnosis of malignant tertian malaria is a matter of the first importance, so that specific therapy may be started with the least possible delay. In recent years the development of modern methods of rapid transport has made it all the more imperative that medical men in all parts of the world should be familiar with the many diverse clinical manifestations of this disease.

My first experience of the difficulties which may be encountered in the diagnosis of *Plasmodium falciparum* infections occurred at an early stage of the 1914-18 war, when I was in charge of a wing of a military hospital in Nairobi. One morning about 80 British soldiers who had been evacuated from the vicinity of Lake Victoria Nyanza and sent down the line by hospital train were admitted under my care. A preliminary examination of these men disclosed a great variety of clinical symptoms, as the result of which I made a number of provisional diagnoses.

Many of the patients were obviously the victims of malaria, but there were others whose symptoms were unlike any which are usually associated with this disease. Several seemed to be suffering from some acute abdominal condition, such as appendicitis, pancreatitis, or biliary colic. Some were passing blood and mucus per rectum, and these I diagnosed as dysentery. Two or three had the clinical appearance of typhoid fever, and there were several with cerebral symptoms which I thought were probably due to heat-stroke. In one case I suspected amoebic hepatitis and in others bronchitis or bronchopneumonia. A blood smear was taken from each patient as a routine procedure and sent to the laboratory for examination; the presence of malignant tertian malaria parasites was reported in every single instance. The administration of quinine, at that time the only antimalarial drug available, was followed in all cases by prompt alleviation of symptoms and ultimate recovery.

My object in recounting this incident is to impress on those who are about to practise in malarious regions or to sail in ships which may touch at ports where the disease is endemic that malignant tertian infections often fail to conform to the popular conception of malarial fever. They may simulate a great variety of other diseases, and failure to recognize this fact has resulted in the loss of many lives which could have been saved by the prompt application of

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specific antimalaria treatment. In the past 12 months two striking examples illustrating this point have come to my notice.

Illustrative Cases

The first case was that of a young woman who visited the Victoria Falls in the course of a holiday tour in South Africa and fell ill with headache and a slight rise of temperature some 10 days later. She had no idea that she had been exposed to the risk of malarial infection, and treated herself for several days with aspirin and other non-specific drugs. Soon after reaching Johannesburg her condition suddenly became critical, and she was admitted to hospital suffering from cerebral malaria, as the result of which she died in spite of all efforts to save her life.

The other case was that of a stewardess employed in a ship on the outward run from London to Capetown. Her illness began in very much the same manner about 10 days after leaving the port of Beira, on the East African coast. Several of the crew were down with malaria, and owing to shortage of nursing staff she continued to attend to them for several days before reporting sick. When she did so, the ship's surgeon, who had had no previous experience of tropical diseases, made a provisional diagnosis of influenza and prescribed codeine. She was ultimately sent ashore at Capetown in a comatose condition and admitted to hospital. A blood smear revealed a very heavy infection with *P. falciparum*, and she was given immediate parenteral treatment with antimalarial drugs. This case fortunately ended in recovery, though during the first 24 hours after admission her condition was the cause of grave anxiety.

These two cases illustrate two characteristic features of malignant tertian malaria: (1) that the disease often has an insidious onset, and (2) that in the absence of specific treatment the patient may with little or no warning become critically ill with so-called "pernicious" symptoms, which have been variously classified as cerebral, algid, bilious, remittent, pneumonic, and cardiac. More often than not the paroxysm is ill defined and rigors are exceptional, the temperature rarely exceeding 104° F. (40° C.). A double peak in the temperature chart owing to the segmentation of two groups of parasites is common, and there may be three, four, or more groups, each segmenting independently and giving rise to continuous fever, with several peaks in the 24 hours.

It is important also to recognize that in a primary case parasites may be so scanty in the peripheral blood during the first few days of fever that they may not be detectable in a blood smear, even if no antimalarial drug has been administered. A negative smear, particularly if this has been taken at the height of the fever, should not therefore be regarded as excluding the possibility of malarial infection. The wisest course in such cases is to administer an antimalarial drug and to take another blood smear immediately the temperature drops, when it is often possible to confirm the diagnosis.

Mode of Action of Antimalarial Drugs

It is necessary to consider this subject in relation to the various phases in the life-cycle of the malaria parasite in the human body. The recent demonstration by Shortt and his co-workers of an exo-erythrocytic phase of *Plasmodium cynomolgi* in the monkey and of *P. vivax* in man, and the subinoculation experiments of Fairley and his colleagues in Australia, have greatly clarified our knowledge of this problem, which had been for so many years a matter of speculation (Shortt and Garnham, 1948; Shortt, Garnham, Covell, and Shute, 1948; Fairley *et al.*, 1947).

Antimalarial drugs may act in four possible ways: (a) against the primary tissue, or pre-erythrocytic, phase of the parasite; (b) against the asexual parasites in their ery-

throcytic phase; (c) against the sexual parasites in their erythrocytic phase; and (d) against the hypothetical persistent tissue phase of the parasite, to which latency and late relapse in *vivax* malaria have been attributed (Shannon, 1948). There is convincing evidence against the existence of the last-named stage in *falciparum* infections, and only the first three categories are considered here (see Table).

Table Showing the Action of Various Drugs on *P. falciparum*

Class of Drug	Action on		
	Pre-erythrocytic Phase	Erythrocytic Phase (Asexual Forms)	Erythrocytic Phase (Sexual Forms)
Cinchona alkaloids (e.g., quinine)	—	+	—
9-aminoacridines (e.g., mepacrine)	—	+	—
4-aminoquinolines (e.g., chloroquine, camoquin)	—	+	—
8-aminoquinolines (e.g., pamaquin, pentaquine, isopentaquine)	+	—	+
Biguanides (e.g., proguanil)	+	+	—*
Sulphonamides (e.g., sulphapyrazine, sulphamerazine)	—	+	—

* But prevents completion of development in the mosquito.

The cinchona alkaloids, the 9-aminoacridines, and the 4-aminoquinolines have a destructive action on the asexual parasites of all forms of human malaria in the erythrocytic phase. The sulphonamides also act on this phase in *falciparum* infections, but in view of the risk of toxic effects, particularly of agranulocytosis, this class of drugs is not generally recommended for the routine treatment of malaria. Findlay (1949), however, recorded a complete absence of toxic reactions in a group of 441 British troops in West Africa who were given a daily dose of 50 mg. of sulphapyrazine, sulphamerazine, or sulphamezathine over a period of 12 months or more, the first-named giving results superior to those with mepacrine in the prophylaxis of malaria. He suggested that the sulphonamides might be found useful for this purpose should the local strains of parasite prove refractory to other drugs, or in a case of idiosyncrasy to other drugs.

The 8-aminoquinolines do not affect the asexual parasites in the erythrocytic phase, but exert a powerful destructive action on the gametocytes. They also act on the pre-erythrocytic phase, but only when employed in dosage dangerously high for routine use. The biguanides are the only known class of drugs which can be used with safety against this phase of the parasitic cycle. They also act on the asexual forms in the erythrocytic phase. They have no demonstrable effect on the gametocytes in the peripheral blood, but render them incapable of completing their development in the mosquito.

Prophylactic Treatment

The drugs used in the prophylaxis of malaria fall into two categories: (a) true causal prophylactics, which act on the parasite in its pre-erythrocytic phase; and (b) schizonticidal drugs, which destroy the asexual forms of the parasite in the erythrocytic phase and thus suppress the overt attack.

As stated above, the only drugs at present available which exert a true causal prophylactic action against malignant tertian malaria in non-toxic dosage are the biguanides, of which the best-known example is proguanil ("paludrine"). The dosage of proguanil recommended for prophylaxis is 100 mg. daily for non-immune individuals, and 300 mg. in a single dose once weekly for indigenous inhabitants of malarious countries. A great advantage of this drug is that

it can be placed in the hands of laymen for distribution without risk of ill effect, even should the prescribed dose be grossly exceeded.

The second, or suppressant, group of drugs includes the cinchona alkaloids, the 9-aminoacridines, and the 4-aminoquinolines. For the effective suppression of *falciparum* malaria quinine has to be administered in doses of as much as 10 gr. (0.65 g.) daily, which is the maximum that can be tolerated over a prolonged period. Against New Guinea strains of *P. falciparum* even this dosage has been found insufficient, failing to prevent overt attacks during the period of its administration. Apart from the unpleasant side-effects caused by the prolonged administration of quinine, the association of this drug with the precipitation of blackwater fever renders it undesirable for use as a suppressant in *falciparum* infections.

Mepacrine, in a dosage of 100 mg. daily, is a very effective suppressant of malignant tertian malaria, provided that the drug is taken for 14 days before exposure to infection and continued for one month after leaving the endemic area. It produces radical cure by schizonticidal action, destroying the young asexual parasites after their entry into the blood stream. The dramatic fall in malaria casualties during the later stages of the 1939-45 war in the South-West Pacific and in South-East Asia was chiefly due to the general adoption of mepacrine prophylaxis by the Allied Forces, and the rigid enforcement of this measure was an important factor in bringing about the successful conclusion of both these campaigns. It should be noted that neither proguanil nor chloroquine became available for general use until after the termination of hostilities.

Despite its powerful suppressant action, mepacrine has certain disadvantages which militate against its routine use under peacetime conditions. During the first 10 to 14 days of suppressive treatment a variable degree of nausea and abdominal discomfort is not uncommon. These symptoms usually disappear completely, but* persist to some extent in a small proportion of cases. Headache, insomnia, and temporary giddiness may also occur during this stage, but are less frequent. When taking the drug over prolonged periods a proportion of individuals develop skin lesions, the most common of which is a lichenoid dermatitis affecting chiefly the hands and wrists and feet and ankles. Yellow discoloration of the skin is comparatively common; this is of no great moment among troops in time of war, but is a distinct disadvantage under peacetime conditions, particularly where women are concerned.

Chloroquine is a powerful suppressant, and excellent results have been reported with a dosage of 300 mg. of the base* administered in a single dose once weekly. Its action is similar to that of mepacrine, but it is said to be considerably less toxic and does not discolour the skin. The same advantages are claimed for camoquin, with a dosage of 500 mg. weekly.

At present the choice of drug for prophylactic use would seem to lie between proguanil and either chloroquine or camoquin. The stage in the parasitic life-cycle on which the drug exerts its action is of little interest to the individual under treatment, provided that the overt attack is prevented without any injurious side-effects, and from this point of view there is little to choose between the two classes of drugs. Chloroquine and camoquin, however, do not possess the very low grade of toxicity which is so remarkable a property of proguanil, rendering the last-named drug particularly suitable for widespread admin-

istration among labour forces or other employees recruited from indigenous populations.

Treatment of the Clinical Attack

Most of the literature relating to the chemotherapy of malaria published during the last few years has been based on work initiated during the war period, when the overriding objective was the maintenance of the largest possible proportion of troops in a fit condition for the conduct of military operations. We have become accustomed to relate all our activities to their effect on the war effort, and it is not always appreciated that the objects of therapy in peacetime differ in certain important respects from those obtaining in time of war. Thus, in wartime minor toxic manifestations of drugs, or even an occasional case of severe toxicity, are of no great significance, since they do not affect the fighting efficiency of the troops to any appreciable extent. But in peacetime such occurrences are of very considerable importance, both to the patient and to the physician in charge of the case.

Again, in wartime a system of treatment which will control the clinical attack and effect radical cure in the great majority of malignant tertian infections may be considered adequate. But under peacetime conditions no treatment for this disease can be considered satisfactory unless it will ensure rapid alleviation of symptoms and a high rate of radical cure, not only in the "average" case but also in abnormally susceptible individuals exposed to heavy and repeated infection in hyperendemic areas. Finally, the provision of adequate treatment for indigenous populations, which is seldom practicable whilst military operations are in progress, is usually a major feature of antimalarial campaigns undertaken in times of peace.

Specific Treatment

The principal objects in the treatment of malignant tertian malaria are the termination of the clinical attack with the least possible delay, radical cure of the infection, minimum toxicity on the part of the drugs employed, and sterilization of gametocytes, so that mosquitoes which feed on patients during or after the attack cannot transmit the disease to other individuals.

Daily dosage of 20 to 30 gr. (1.3 to 2 g.) of quinine over a period of seven to ten days will usually bring about a rapid termination of the clinical attack and a high rate of radical cure. It is, however, comparatively ineffective against infections with certain European strains of *P. falciparum*. For example, James, Nicol, and Shute (1932) found that the amount of quinine necessary to control a primary attack of malignant tertian malaria caused by strains originating in the Roman Campagna and Sardinia was eight times as great as that required for infections with Indian strains of the same species of parasite. Quinine has no effect on the infectivity of gametocytes to mosquitoes, but a more serious disadvantage is that it may act as a contributory factor in the precipitation of blackwater fever. There was a striking reduction in the incidence of this disease among British troops stationed in West Africa after the substitution of mepacrine for quinine in the prophylaxis and treatment of *falciparum* infections (Findlay and Stevenson, 1944).

Mepacrine, when administered in the dosage now usually prescribed—i.e., beginning with a "loading" dose of 600 to 900 mg. on the first day or first two days of treatment, and continuing at 300 mg. daily for five to seven days—will effect a rapid termination of the clinical attack and a high radical cure rate in *falciparum* infections. The rapidity

* = 500 mg. of the diphosphate salt.

with which this drug resolves the clinical symptoms of malaria has not in the past been fully appreciated, because until comparatively recently it has been the usual practice to prescribe a maximum of 100 mg. daily throughout the course, without a preliminary loading dose. Mepacrine does not, however, sterilize gametocytes; moreover, its toxic side-effects, though of rare occurrence, are by no means negligible. This applies particularly to the so-called mepacrine psychosis, which may be attended by symptoms of mental aberration or even of maniacal excitement (Findlay, 1947).

Chloroquine, like mepacrine, brings about rapid alleviation of clinical symptoms and a high rate of radical cure. It is said to be superior to both mepacrine and quinine in the treatment of *falciparum* infections, and to be relatively non-toxic in therapeutic dosage (Earle and Berliner, 1948). It has the advantage over mepacrine of not tinting the skin, and of being less likely to induce disagreeable gastro-intestinal symptoms. The regime recommended for adults is an initial dose of 600 mg. of the base, followed by an additional 300 mg. on each of the two following days. Camoquin, whose action resembles that of chloroquine, has been given in doses up to 400 mg. thrice daily for five days. Good results have also been reported with a single dose of 600–1,000 mg. Neither of these drugs renders gametocytes non-infective to mosquitoes.

Proguanil, in the absence of reinforcement with other drugs, has a less rapid action on the clinical attack than mepacrine, quinine, or chloroquine. Fairley *et al.* (1946a) recorded a high radical cure rate with New Guinea strains of *P. falciparum*, following a 10-days course of 300 mg. of proguanil daily; but against infections with a West African strain the drug failed to effect radical cure even when the daily dosage was raised to 600 mg. (Covell, Nicol, Shute, and Maryon, 1949). Reports from India, Malaya, Southern Europe, the Sudan, and Central Africa indicate that in these countries also there exist strains of *P. falciparum* which tend to recrudescence after a full therapeutic course of proguanil. The drug effectually sterilizes the gametocytes of *P. falciparum*, a property not possessed by mepacrine, chloroquine, camoquin, or the cinchona alkaloids. As already noted, it is by far the least toxic of all known antimalarial drugs.

As regards the choice of drug for treatment of the attack, none of those at present available fulfils all the requirements postulated above. Quinine has the disadvantage of its association with the precipitation of blackwater fever and is comparatively ineffective against certain geographical strains of *P. falciparum*. Mepacrine has a rapid and effective schizonticidal action, but is apt to produce a number of minor toxic manifestations and occasional psychoses of a more serious nature. Chloroquine and camoquin are probably the most powerful schizonticides, but occasional toxic manifestations have been recorded with each of them. None of these drugs renders gametocytes non-infective to mosquitoes.

Proguanil has a very low degree of toxicity and effectually sterilizes gametocytes, but, as we have seen, in the absence of reinforcement its action on the clinical attack is comparatively slow, and it cannot be relied upon to effect radical cure. It has, however, been demonstrated that when reinforced by mepacrine on the first day of treatment both these disadvantages can be overcome (Covell *et al.*, 1949). The dosage employed was 300 mg. of proguanil twice daily for 10 days, reinforced with 900 mg. of mepacrine given in three doses on the first day of treatment. It is possible that reinforcement by only

600 mg. of mepacrine would prove equally effective. It is considered unlikely that a single day's medication with this drug would be attended with any injurious side-effects, and it therefore seems probable that the above system of treatment would fulfil the main requirements for the treatment of malignant tertian malaria—namely, rapid alleviation of clinical symptoms, a high rate of radical cure, and sterilization of gametocytes, with minimal risk of injurious side-effects.

Reinforcement of the proguanil course with chloroquine or camoquin in place of mepacrine would probably prove at least as effective and might indeed prove superior. It is hoped that evidence on this point will shortly be forthcoming. Whatever form of treatment is adopted for the clinical attack, it is advisable to follow this up with a weekly maintenance dose of proguanil, chloroquine, or camoquin (100 mg. in each case) for six weeks to cover the period when recrudescences are most likely to occur.

For the dispensary treatment of indigenous populations in malarious countries, who possess some degree of tolerance to malarial infections, a single-dose treatment of 300 mg. of proguanil or chloroquine base or 600–1,000 mg. of camoquin has proved effective in a number of field trials. Chloroquine and camoquin are the more powerful schizonticides, but the exceedingly low toxicity of proguanil and its present comparatively low market price are powerful arguments in its favour. The extent to which each of these drugs is used will no doubt be determined very largely by the price at which they are eventually made available.

Allusion has already been made to the fact that different strains of *P. falciparum* may vary widely in their response to treatment with the same antimalarial drug. The Italian and Sardinian strains found by James, Nicol, and Shute (1932) to be resistant to quinine were readily susceptible to mepacrine. Similarly, Fairley *et al.* (1946b) encountered a strain of *P. falciparum* at Wewak, New Guinea, which proved resistant to mepacrine but highly susceptible to proguanil. The existence of strains which are naturally resistant or have acquired resistance to the action of proguanil has also been reported. It is therefore unwise to be dogmatic about the most suitable remedy for use against malignant tertian malaria in any particular circumstances, and it is fortunate that we now have at our disposal several specific antimalarial drugs, so that should a strain of parasite resistant to one of them be encountered it may be replaced or reinforced by one of the others.

General and Emergent Treatment

Whatever specific treatment is prescribed, the patient should be confined to bed during the attack and the bowels kept open by small doses of calomel, followed by salts in the morning if found necessary. The diet should be restricted to fluids during the height of the fever, glucose being given freely if available. In the event of a rigor, hot-water bottles and several blankets are indicated. Hyperpyrexia may necessitate cold sponging. The headache may be relieved by aspirin, caffeine, codeine compound, or phenobarbitone.

Pernicious forms of malignant tertian malaria, whether cerebral, algid, or gastro-intestinal, require special treatment. In such cases the oral administration of drugs is seldom practicable, and, since prompt action is necessary to save the patient's life, they must be given parenterally. Quinine dihydrobromide or dihydrochloride, 10 gr. (0.65 g.) in 20 ml. of normal saline, may be injected intravenously very slowly, not more than 2 ml. per minute by the watch.

repeated in six to eight hours if necessary. Mepacrine sulphionate (atebrin musonate) may also be given intravenously, but the margin of safety with this drug is low, and the intramuscular route is to be preferred, 200 mg. being injected into each buttock (total dosage 400 mg.). Good results have also been claimed with chloroquine and camoquin given intramuscularly. Should none of the above-mentioned drugs be available, quinine sulphate 15 to 30 gr. (1 to 2 g.) may be given per rectum, mixed with starch paste thin enough to run through a rectal catheter. The drug is rapidly absorbed by this route. As soon as the patient is able to take drugs by mouth all further medication should be administered orally. The action of proguanil is not sufficiently rapid to warrant the use of this drug in cases of extreme urgency.

Blood transfusion may be indicated in pernicious malaria accompanied by grave anaemia. Vomiting, if persistent, may be relieved by intravenous injections of 5% glucose in 200 to 400 ml. of normal saline, repeated if necessary, and supplemented by 1 mg. of thiamin hydrochloride for each 25 g. of glucose.

Summary

The relative merits of the various specific drugs now available for the treatment of malignant tertian malaria are discussed in detail.

Emphasis is laid on the importance of differentiating this disease from a number of others which it may simulate very closely, and on the fact that infections with different geographical strains of *P. falciparum* may vary widely in their response to treatment with the same antimalarial drug.

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The control of venereal diseases in Germany was one of the most arduous tasks which faced the Occupation Authorities after the war. In an article which appeared in a recent number of the *Epidemiological and Vital Statistics Report*, Dr. T. Guthe, Chief of the Venereal-Disease Section of WHO, surveyed the situation in Germany from 1945 to 1948, and gave a detailed account of the result of measures taken in the various zones during that period. According to the *Chronicle of the World Health Organization* the venereal-disease problem in Germany is not due to the presence of occupying troops and displaced persons, although this view is often expressed by Germans. Venereal diseases increased steadily in Germany, as in other countries, as a consequence of war conditions: displacement of civilian, industrial, and military populations; social, economic, and political upheavals; disruption of family life; increase of promiscuity and prostitution. Surveys carried out at Frankfurt-on-Main and Hamburg show that venereal diseases caused considerable ravages among the civilian population during the war. The increase in venereal infections which took place during the war in civilian and military populations in the Reich was also observed in several countries occupied by or allied with Germany, as recorded in Denmark, Finland, France, Greece, Norway, and some of the Balkan countries.

CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS, SURGERY, AND THERAPEUTICS*

BY

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The extradural administration of local analgesic solutions through the sacral hiatus via an indwelling malleable needle or an indwelling small-bore catheter is designated as continuous caudal analgesia. The basic technique of single-injection caudal analgesia produced by a cocaine solution was independently introduced in Paris in 1901 by J. A. Sicard and F. Cathelin. As new and safer local analgesic agents were developed, modifications of the technique greatly extended the anatomical application of this method to nerves of pain in, first, the sacral plexus, then the lumbar region, and, finally, to the low and mid-thoracic regions. Even though caudal analgesia provided a high percentage of successes in rectal surgery and in urology, it was so undependable in obstetrics that Stoeckel abandoned it shortly after he introduced it in 1909. Dr. Hans Schlimpert, of the Freiburg Clinic, developed a satisfactory technique of caudal analgesia in obstetrics, which was used in combination with *Dämmerschlaf*. His tour of American clinics in 1913 stimulated the application of this method in a few centres.

In America during the next three decades the single-injection technique of caudal analgesia was enthusiastically utilized but ultimately rejected by all except one of its outstanding advocates. The one exception was my own revered professor of anaesthetics, Dr. John S. Lundy, of the Mayo Clinic. It was Lundy who instructed me in my first applications of this technique. It was he who inspired me with the thought that all pain can be conquered if the physician will master the science of applying the principles of pharmacology and anaesthesiology to the specific anatomical pathways of pain.

Thus in 1940 and 1941, when uncontrolled obstetric pain on the one hand, and profound and prolonged obstetric narcosis on the other, demanded a more satisfactory and safer method of anaesthesia for the parturient woman and her baby, Southworth, Edwards, and I surveyed the problem to determine the specific nerve pathways involved. We found that the classic researches of John G. P. Cleland, of McGill, had delineated the afferent pain pathways of the contracting uterus as passing through the eleventh and twelfth thoracic nerves. We substantiated the postulates of Sir Henry Head, of England, that pain of the dilating cervix was transmitted through the second, third, and fourth sacral nerves. We concurred with DeLee, Greenhill, and Tucker that the pain of perineal distension was transmitted through the pudendal, perineal, and haemorrhoidal nerves. We soon found that the single-injection technique of Sicard and Cathelin when extended to the tenth thoracic segment in the peridural space would totally relieve temporarily the pain of labour or the pain of delivery.

Merely by combining the principles of caudal analgesia with the continuous spinal anaesthesia principle of Lemmon, of Philadelphia, and the continuous aortic lumbar anaesthesia of Abrucl, of Rumania, we were able to fashion a

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