GERHARD DOMAGK

Further progress in chemotherapy of bacterial infections

Nobel Lecture, December 12, 1947

Excellency, honoured colleagues, I am unable to express my profound gratitude for the high honour conferred upon me in the award of the Nobel Prize for Physiology or Medicine for 1939 - which I was not allowed to accept at the time - in any other way than by reporting on the further developments in the field which had then just been opened up.

The first decisive phase was the discovery of the curative action of certain sulphonamide-containing azo compounds, which had been synthesized by Klarer and Mietzsch. The most effective of these had taken their place under the names *Prontosil rubrum* and *Prontosil solubile* in the armoury against the streptococcal infections of man. This first phase was surveyed by Professor Nanna Svartz in *Les Prix Nobel en 1939.*

The problem of chemotherapy of bacterial infections could be solved neither by the experimental medical research worker nor by the chemist alone, but only by the two together working in very close cooperation over many years. I therefore feel under a profound obligation, in view of the high honour which has been conferred upon me as one who has taken part in such collaboration, to pay tribute to all my colleagues. In particular I must mention the two chemists Dr. Mietzsch and Dr. Klarer who, thanks to the substances produced by them, enabled me to discover the curative action against bacterial infections after I had worked out and extended step by step, entirely on my own initiative, all possible methods oftesting. Convinced that a way could be found I had persevered with this work over a period of many years, despite all the scepticism prevailing in this sphere. I should also like to express my gratitude for the advice given to me by the pharmacologist Dr. Hecht. I am particularly fortunate in having had these experienced and well-tried colleagues, who were mentioned in 1935 in the first article "Ein Beitrag zur Chemotherapie der bakteriellen Infektionen" (A contribution to the chemotherapy of bacterial infections), published in the *Deutsche Medizinische Wochenschrift* (1935), and in having been able, with them, to continue the work to this day in the field which at that time had been newly opened up

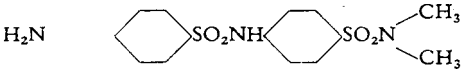
and to discover still further therapeutically valuable anti-bacterial sulphonamides. I should also like to thank many other loyal colleagues who assisted me with my investigations, often under dangerous conditions, with the greatest industry and infinite patience. At the same time, I wish to express sincere thanks to all clinicians and colleagues who have helped to apply the experimental results in practice for the benefit of patients. I also have to thank farsighted men of industry who made it possible for me to set up a laboratory where I was able to carry out my work on the requisite scale. I recall with particular gratitude the magnificent help given me by Professor Horlein. Unfortunately many difficulties stood in the way of our work during and after the war, difficulties with which to some extent we still have to contend. Nevertheless the management of the Bayer Wuppertal-Elberfeld dye factories always found ways and means of supporting us - who were engaged in scientific research - indeed, they assisted us far more than did the state, whose first duty it should in fact have been to help its citizens, through research, to combat disease. And this shows the high sense of responsibility of enterprises created and built up by the energy of great personalities such as Friedrich Bayer, Carl Duisberg, and Heinrich Horlein. Few if any sickness funds or insurance companies have shown such a great sense of responsibility or such a sense of duty to the community in the carrying-out of work at the research establishments maintained by them, despite the fact that these institutions are under a greater obligation to look after the healthand welfare of their members, and mostly have much more capital at their disposal. The Rockefeller Institute in America and throughout the world, and the Kaiser Wilhelm Institutes in Germany were created by responsible individuals. We are and always shall be deeply indebted to these great men - and foremost among them Alfred Nobel - for what they have done for the advancement of science. Nowhere does science enjoy such respect as in this hospitable land of Sweden. We thank this country, its Royal Family and our Swedish colleagues most sincerely for what they do each year on the anniversary of Alfred Nobel's death, on 10th December, in the striving towards true humanism, towards the building of a new and better world and towards a peaceful understanding between nations. May this land one day be rewarded for its services in this field to the entire world and may other states follow this example in noble and peaceful competition.

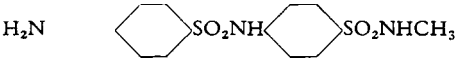
In spirit I bow in reverence before my old teachers at the German universities who equipped me to carry out the work for which you have honoured me, on the further development of which I wish to report now. Within the

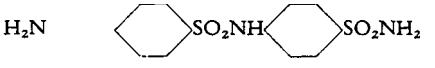
time at my disposal I can draw attention only to the principal phases in the development of chemotherapy as I see them at present and as they emerge from our work. Even the numerous compounds tested with experimental streptococcal infections during the first phase of the development revealed important laws, which have proved of value to all subsequent workers in the sulphonamide field. It was found, in fact, that only those compounds which contained the sulphonamide group in the *para*-position in relation to the group containing nitrogen were of therapeutic value, whereas compounds with the sulphonamide group in the *ortho*- or meta-position were found to be inactive.

Prompted by the German publications on Prontosil - but independently of our own as yet unpublished experiments which were conducted with a view to discovering colourless active sulphonamides outside the azo series - Tréfouël, Tréfouël, Nitti and Bovet began to study the same problem. We are indebted to these authors for having drawn attention for the first time in literature to the fact that 4-aminobenzenesulphonamide, which Mietzsch and Klarer had used as initial material for the synthesis of their sulphonamide-containing azo compounds, was therapeutically active as such. This substance was later used in practice as *Prontosil album, Prontalbin,* and *Sulphanilamide.*

It was again Klarer and Mietzsch who initiated a further phase in the development of chemotherapy of bacterial infections by placing at my disposal substances in which the sulphonamide group is no longer unsubstituted, as in the Prontosil compounds, but is modified by an organic radical with replacement of a hydrogen atom. In the case of substances of this type I discovered the action against staphylococci and pneumococci; although there had been a hint of this in Prontosil, which had been reported by me as far back as 1935, it was now considerably increased. Furthermore, I now established for the first time that such compounds, known under the names

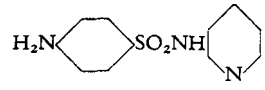
Uliron 

Uliron B (Neo-Uliron)  and

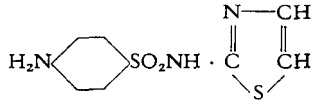
Uliron C 

had a noteworthy effect upon gonococci. The Uliron compounds were the first sulphonamide compounds used in Germany against gonorrhoea after the experiments with Prontosil compounds had proved unsatisfactory.

A further improvement in the action against staphylococci, pneumococci, and gonococci was brought about by introducing a heterocyclic ring in place of the hydrogen in the SO_2NH_2 group. A series of such compounds had already been made available at an early date by Mietzsch and Klarer; however, an intensive study of this field - this time in all advanced countries throughout the world - began only when

Sulphapyridine = M. & B.693  *p*-aminobenzenesulphonamidopyridine,

which had been synthesized by Philipps and Evans, was shown in England by Whitby's experiments to have an effect on pneumococcal infections going beyond that produced by the Prontosil compounds; the broad experience of British clinicians very soon confirmed this experimental finding. This sulphapyridine compound is still in use today in the treatment of lobar forms of pneumonia, but has been superseded more and more by sulphathiazole - subsequently also known by the names Cibazol and Eleudron - which are approximately equally effective against pneumococci and meningococci and still more effective against staphylococci and gonococci, since it very frequently, especially when administered in large doses, causes serious stomach disorders and vomiting. Sulphathiazole



or *p*-aminobenzenesulphonamidothiazole, was produced and a patent was applied for in respect of it independently by several people, but first by Hartmann and Merz. So far sulphathiazole has firmly held its position, although its efficacy in the case of gonorrhoea has progressively declined. For a time people used to speak of a "lightning cure" for gonorrhoea, but ultimately the results became less and less satisfactory although the doses were continually increased. This fact is too well known to require any detailed explanation by me. But we should learn from this undeniable fact and should try to discover the reasons for it. At first the failures were attributed to anatomical causes. People used to speak of the role of sites difficult to reach ("Hohlraumeffekt"), etc. But this explanation was unsatisfactory and was not sufficient for all cases. Then it was thought that the war might have reduced the patients' resistance, but this explanation likewise did not always hold good. I have

constantly emphasized that cooperation by the body is an important factor with any sulphonamide treatment. We all remember how at the beginning of the sulphonamide era it was repeatedly observed that fresh cases of gonorrhoea in men responded best to sulphonamide treatment when suppuration had already occurred for several days, and not at the first appearance of the disease. Perhaps the lowering of natural resistance due to war-time conditions explains why a considerable falling-off in the successes in Germany should to some extent have occurred at a time when optimum results were still being obtained in Switzerland. With the present catastrophic shortage of protein in the diet many patients probably find it difficult to make up the protein losses due to the destruction of leucocytes resulting from an inflammatory condition. However, these facts alone are not sufficient to explain the number of failures. Introduction of resistant strains due to the general upheaval during and after the war was therefore suspected. Finally the question whether gonococci might, like protozoa, possibly become resistant to the drug during treatment was discussed. We ourselves never succeeded in rendering a strain sulphonamide-resistant by treating with small doses of sulphonamide under experimental conditions. However, if this phenomenon should occur in very exceptional cases this would in no way explain the great number of failures. Of decisive importance for a clarification of this question, however, is the fact, which was established by Felke at the beginning of the sulphonamide era, that gonococcal strains of widely differing sensitivity existed from the outset. Felke distinguished strains which would grow on ascites plates with 0.6, 1.2, 2.5, and even 5 mg% Uliron C. It is noteworthy that the clinical failures occurred in the case of carriers of highly resistant strains. Hagerman (Lund) determined the different degrees of resistance of gonococci by another method. He dripped graduated concentrations of sulphonamide solutions on to a kind of ascites agar plates, allowed the drops to be absorbed and then inoculated the plates uniformly with one strain. He expressed the resistance to sulphathiazole by the numbers 0-11. o denoted the highest concentration, 1 : 200; and 11 the lowest, ca.1 : 400,000. He came to the following conclusion: In the case of gonorrhoea which has been treated with sulphathiazole the prognosis depends mainly on the resistance to sulphonamides of the gonococcal strain in question. In any particular case of gonorrhoea the prognosis can be made with great reliability by means of chemoresistance determinations in vitro. Later Schmith (Copenhagen) also settled satisfactorily the question of primarily resistant strains. He tested 50 old strains from the pre-sulphonamide era; among these he found approx-

imately the same resistance percentage ratio as he had found with his fresh strains. There can therefore be no doubt that even before the sulphonamide era there were gonococcal strains with a high primary resistance. The resistant strains therefore existed before the sulphonamide era and have not come about as a result of sulphonamide treatment with insufficient doses, or any similar cause. They are due to natural selection. The spread of these resistant strains would have been avoided if the few patients who were carriers of them in 1937 had received careful treatment and had been subjected to clinical supervision until their cure was absolutely certain. But this was not done.

Today we are faced with the same question with regard to the use of penicillin. If we are not to suffer the same disappointment at some future time, the patients with resistant strains must be kept under treatment until they have been definitely cured. Felke rightly maintains that gonorrhoea will not be eradicated - even if we have the best remedies at our disposal - until a woman infected with gonococci is not given a clean bill of health before a cervical culture has been grown. In women the reservoir of the gonococcus is not primarily the urethra but the uterus, and especially the tube angles when the adnexa are affected. Felke describes treatment of gonorrhoea in women without the growing of a culture as anachronistic. This applies in particular to determination of the female infection sources. Jadassohn's view that the culture should be used only in doubtful cases is not longer valid. The superiority of the culture over microscopic examinations has once again been shown very recently by Veltman of the Grütz clinic (Z. *Haut-Geschlechtsbank.*, No. 7 (1947) 203). He found positive cultures in 52 cases following completion of a course of penicillin treatment in hospital and negative microscopic findings. He reports that in the course of a year 86 patients would have been discharged from the clinic as cured if culturing had not made it possible to prove the presence of gonococci. The culturing method - at least in the case of women - is therefore absolutely necessary in addition to microscopic examination, since it is more efficient than microscopic examination alone. Now that penicillin treatment, with the follow-up period reduced to 5 days has been introduced, an additional examination by the cultural method is in fact very important. Since relapses after penicillin treatment do not usually occur until after the first 3 days, at least one culture should be taken a week after completion of the treatment. Otherwise one would be only too justified in asking, as Clarke recently did: "Penicillin: help or hindrance in venereal disease control?", for we already see the first signs that, if treated patients are not subjected to a very thorough check-up,

penicillin - like the sulphonamides - is being misused, with the inevitable result that resistant strains will survive and then spread. Huriez and Desurmont (Lille) have already drawn attention to the fact that since October 1946 there has been a distinct decline in successes with penicillin, which has necessitated the combination of penicillin with fever, with sulphonamides and local treatment *(Presse Med., No.* 2 (1937), Ref. Z. Haut-Geschlechtskrank. No. 2 (1947) 217-218). If the spread, through natural selection, of still more resistant strains of gonococcus is to be avoided in future, these demands for a particularly careful check on treated patients will not have to be overlooked, irrespective of whether sulphonamides or penicillin are used. This is in no way to say that the use of sulphonamides in the treatment of gonorrhoea should now be completely abandoned. Hopf of Hamburg recently stated that in Hamburg and northern Germany 70% of fresh cases of gonorrhoea were still being cured at the first attempt by intensive treatment with Eleudron or Cibazol, administered at the rate of 6 g each day for 3-5 days. According to this report the number of sulphonamide-resistant strains in Hamburg and northern Germany is smaller than in other areas. Hopf described the sulphonamides as indispensable for the treatment of relapses, even after penicillin. Schreus reported in 1946 that he had obtained the best results with injections of sterile milk and 3 x 5 tablets of Eleudron for 2 days. After the first course of intensive treatment 75% were free from gonococci, after the second the figure was 90.8%. Of the remaining uncured patients a further 80%. could be cured with a combination of sulphonamides and Olobinthin, which meant that only 2% resistant cases remained. Felke found that if a second course of treatment with penicillin was necessary it should always be combined with a three-day course of massive doses of sulphonamide, with 200,000 units penicillin given on the second day of the usual intensive course of sulphonamide treatment.

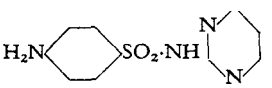
Why some gonococcal strains are more resistant than others is still not clear. It is suspected that some gonococcal strains, like some staphylococcal strains, can produce more *p*-aminobenzoic acid or other antisulphonamide factors. This possibility might be suggested by our observation that certain gonococcal strains are inhibited to a greater extent by Marbadal - the sulphathiourea salt of Marfanil - and Supronal (the effectiveness of which is well known to be only partially impaired, if at all, by *p*-aminobenzoic acid) than by Eleudron. It would therefore appear possible that the 100% success achieved by Bernhard in the treatment of gonorrhoea in women may to some extent be due to this, and not merely to the fact that higher doses are possible

thanks to better tolerance. Another way of achieving better results might be to find pyretic agents which would bring about moderate degrees of fever for a relatively long period, on the same lines as typhoid bacillus vaccines. A rise in body temperature during sulphonamide treatment intensifies the biochemical reaction between drug and pathogen, while at the same time the heat itself injures the heat-sensitive gonococci. According to Felke 1°C above normal, extending over a sufficiently long period, is enough. Intensive courses of Pyrifer treatment are too short-lasting to give the optimum results, and this is no doubt the main reason why 40% Olobinthin, which usually gives slight pyrexia lasting 3-4 days, is superior. Boas and Marcussen gave 10 x 1g sulphathiazole for 3 days and on the third day induced fever for a period of 5-5½: hours by hyperthermia. Of 20 patients, 19 were cured *(Ugeskrift Laeger,* 106 (1944) 16).

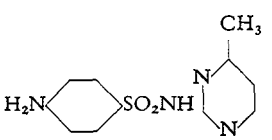
During the past few years we have often been too easy-going with sulphonamide treatment of gonorrhoea, giving 2 Eleudron tablets 5 times a day at intervals of 2 hours. With this regimen adequate blood and tissue concentration was achieved for only a small part of the day, whereas during the rest of the day and during the night the cocci could recover. Intervals between individual doses should not exceed 4-6 hours.

All other specialized fields of medicine have learnt from dermatology, in which massive doses of sulphonamides were given consistently at 4-6 hourly intervals, and massive doses over a short period are now the rule in the treatment of acute infections of any kind.

For gonococcal infections sulphathiazole has even now not been surpassed by other sulphonamide compounds to any extent worth mentioning. In the case of streptococcal infections, on the other hand, sulphathiazole is greatly surpassed in effectiveness by the sulphapyrimidine compounds, and especially by 2-(*p*-aminobenzenesulphonamido)-pyrimidine



Pyrimal, Debenal, Sulphadiazine and the monomethylated compound



Methyldebenal, Debenal M, Sulphamerazine

The sulphapyrimidine compounds were also developed independently at different laboratories. In the patent literature they were first described by the

Deutsche Hydrierwerke (Hentrich) and by the firm of Schering (Dohrn and Diedrich); the first scientific publication was that of Roblin, Williams, Winnek and English.

The following experiment on mice, which were infected intraperitoneally with β-haemolytic streptococci of group A, illustrates the superiority of sulphapyrimidine compared with experimental infections with haemolytic streptococci of group A :

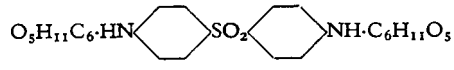
		Number of animals	*Alive 24 hours after infection*	*Survivals*	
Controls		12	0	0	
Prontalbin	0.5 and 5% subcutaneous injection	10	10	1	1
	0.5 and 5% by mouth	10	9	0	
Debenal	0.5 and 5% subcutaneous injection	10	10	5	6
	0.5 and 5% by mouth	10	10	1	

This result is for a single treatment. Where the animals were given three doses - 1, 6, and 24 hours after being infected - the superiority of sulphapyrimidine is even clearer.

		Number of animals	*Alive 24 hours after infection*	*Survivals*	
Controls		12	0	0	
Prontalbin	0.5 and 5% subcutaneous injection	10	9	0	0
	0.5 and 5% by mouth	10	10	0	
Debenal	0.5 and 5% subcutaneous injection	10	10	5	9
	0.5 and 5% by mouth	10	10	4	

Dosage (2 animals in each case) 0.5% 1.0 cc; 5% 0.2; 0.4; 1.0; and 2.0 cc subcutaneously
0.5% 0.5 and 1.0 cc by mouth
5% 0.2cc; 0.5; and 1.0 cc by mouth

Apart from this, with streptococcal infections certain sulphone compounds show specific superiority over all earlier sulphonamides - for instance, Tibatin, galactoside of 4.4'-diaminodiphenylsulphone,



which was synthesized at Elberfeld by Behnisch and Pöhls.

In the following experiments 80 mice, which had been infected intraperitoneally with β-haemolytic streptococci, were given, 10 in each case, 5%. 0.5 and 1 cc per 20 g body weight by mouth Prontalbin, sulphapyridine and sulphathiazole and 0.5 cc and 1.0 cc of a 2.5%. solution by subcutaneous injection for comparison.

Single dose, 3 hours after infection:

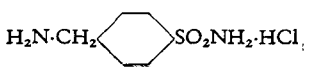
	Number of animals	*Alive 24 hours after infection*	*Alive 48 hours after infection*	*Completely cured*
Controls	14	3	0	0
Prontalbin	20	19	12	1
Sulphapyridine	20	20	16	1
Sulphathiazole	20	20	10	1
Tibatin	20	20	20	10

Three doses, 1, 6, and 24 hours after infection:

Controls	14	4	0	0
Prontalbin	20	17	13	0
Sulphapyridine	20	20	19	1
Sulphathiazole	20	17	15	0
Tibatin	20	20	20	15

Experiments on rabbits also showed Tibatin to be more effective than Prontalbin, sulphapyridine or sulphathiazole. However, these sulphone compounds are distinctly more effective only when introduced parenterally; when administered orally they are unreliable and, obviously owing to uncontrollable decomposition, have undesirable side-effects, such as severe cyanosis, etc.

Whereas the effectiveness of the sulphonamide and sulphone compounds so far considered had been confined almost exclusively to aerobic microorganisms and had as yet shown an observable effect against *Clostridium septicum* infections in only a few cases, e.g. with Uliron compounds, I was able to show a really specific action on anaerobic microorganisms in the case of the compound produced by Klarer:



the hydrochloride of *p*-aminomethylbenzenesulphonamide, later named Marfanil. I look upon this observation as the beginning of a third phase in the fight against bacterial infections with sulphonamides. The action was detectable in vitro as well as in experiments on animals. Although Marfanil and its derivatives were effective against streptococci in vitro but not in animal experiments, the derivatives were occasionally found to have a considerable effect, even in animal experiments, on certain strains of streptococcus which were little affected by other sulphonamides. But their main value does not lie in this direction. Their greatest importance lies in the fact that they can be used in the fight against the most serious wound infections, gas gangrene in man and animals. The experiments which we conducted into the specific effects of Marfanil and its derivatives on the various gas gangrene organisms were repeated, under somewhat modified conditions, by Zeissler. This author used human blood for the culture, whereas we had used rabbit's blood, and the results agreed almost exactly. We will give the results of a few of the experiments conducted by Zeissler to show how sulphathiazole and the other sulphonamides are ineffective in the case of these microorganisms and how, in contrast, the action of Marfanil is specific.

Sulphathiazole.
Clostridium perfringens (*B. welchii*, *B. perfringens*).

Sulphathiazole Microorganisms	*Controls*	*1:1250*	*1:2500*	*1:5000*	*1:10,000*
Concentration	+++++	+++++	+++++	+++++	+++++
1:10	++++	++++	++++	++++	++++
1:100	+++	+++	+++	+++	+++
1:1000	++	++	++	++	++
1:10,000	344	252	248	240	304

Sulphaethylthiodiazole.
Clostridium perfringens (*B. welchii*, *B. perfringens*).

Sulphaethyl-thiodiazole Microorganisms	*Controls*	*1:1250*	*1:2500*	*1:5000*	*1:10,000*
Concentration	+++++	+++++	+++++	+++++	+++++
1:10	++++	++++	++++	++++	++++
1:100	+++	+++	+++	+++	+++
1:1000	++	++	++	++	++
1:10,000	300	308	324	272	356

Marfanil.
Clostridium perfringens (*B. welchii, B. perfringens*).

Marfanil Microorganisms	*Controls*	*1:1250*	*1:2500*	*1:5000*	*1:10,000*	*1:20,000*	*1:40,000*	*1:80,000*
Concentration	+++++	0	0	0	+++++	+++++	+++++	+++++
1:10	++++	0	0	0	++++*	++++	++++	++++
1:100	+++	0	0	0	+++*	+++	+++	+++
1:1000	++	0	0	0	++*	++	++	++
1:10,000	340	0	0	0	196*	320	392	412

(1-day old human blood in agar without glucose)

* No growth after 24 hours incubation but, in contrast to the controls and the other plates, only after 48 hours.

Marfanil is found to be superior with *Clostridium novyi* as well as with *Clostridium perfringens*.

Marfanil.
Clostridium novyi (*B. oedematiens*).

Marfanil Microorganisms	*Controls*	*1:1250*	*1:2500*	*1:5000*	*1:10,000*	*1:20,000*	*1:40,000*	*1:80,000*
Concentration	+++	0	0	0	0	+++	+++	+++
1:10	++	0	0	0	0	++	++	++
1:100	188	0	0	0	0	172	248	228
1:1000	33	0	0	0	0	0	30	68
1:10,000	12	0	0	0	0	0	4	7

Sulphathiazole.
Clostridium novyi (*B. oedematiens*).

Sulphathiazole Microorganisms	*Controls*	*1:1250*	*1:2500*	*1:5000*	*1:10,000*
Concentration	M(atting)	M	M	M	M
1:10	M	M	M	M	M
1:100	M	M	M	M	M
1:1000	M	M	M	M	M
1:10,000	9	15	21	26	14

Whereas no growth of the bacilli is possible at concentrations of 1 : 10,000 or 1 : 20,000 Marfanil depending on the sowing, the microorganisms grow so densely at concentrations of 1 : 1250 sulphathiazole that matting occurs and separate colonies can no longer be counted.

The general effect of Marfanil when administered parenterally or orally is illustrated by the following report:

Mice infected with *Clostridium septicum* by intramuscular injection in the thigh.

	Number of animals	*Number of doses given*	*Alive 24 hours after infection*	*Alive 4 weeks after infection*	
Controls	20	—	3	2	= 10%
Prontalbin	10 subcutaneous injection	1 ×	3	3	
	10 subcutaneous injection	3 ×	2	2	8 = 20%
	10 by mouth	1 ×	2	2	
	10 by mouth	3 ×	2	1	
Uliron C	20 subcutaneous injection	1 ×	8	5	
	20 subcutaneous injection	3 ×	11	7	28 = 35%
	20 by mouth	1 ×	8	7	
	20 by mouth	3 ×	10	9	
Marfanil	20 subcutaneous injection	1 ×	19	17	
	20 subcutaneous injection	3 ×	20	19	66 = 82.5%
	20 by mouth	1 ×	18	14	
	20 by mouth	3 ×	18	16	

Two or four animals were given, by subcutaneous injection or by mouth, 0.1, 0.2, 0.3, 0.5 and 1.0 cc per 20 g body weight of 4% aqueous solutions or suspensions of each preparation. The animals which were given only one dose were treated approx. 2 hours after being infected; those which were

given a total of three doses were treated 2, 8 and 24 hours after being infected.

The efficacy against each of the gas gangrene microorganisms which are pathogenic in man, when applied generally and locally, was evaluated. Timely local application gave by far the best results, as is shown by the following:

Rabbits infected by intramuscular injections of earth containing the spores of the following microorganisms: *Clostridium perfringens, Clostridium novyi, Clostridium septicum, Histolyticus, Gigas.* Earth was left in the wound.

	Number of animals	*Alive 24 hours after infection*	*Alive 1 week after infection*
Controls	6	0	0
Marfanil B locally, also MP* 1 g/kg by mouth	12	12	12
Marfanil B locally, also MP by mouth and gas-gangrene serum	12	12	12

* MP = Marfanil Powder.

Rabbits infected in a wound in the back muscle with earth N III containing the most common and the most dangerous causative agents of gas gangrene, namely *Clostridium perfringens, Clostridium novyi, Clostridium septicum,* and *Histolyticus.*

	Number of animals	*Alive 24 hours after infection*	*Alive 8 days after infection*	*Alive 2 weeks after infection*	*Alive 3 weeks after infection*
Controls	8	0	0	0	0
Gas-gangrene serum of maximum potency 1 cc/kg intravenously immediately after infection	4	1	0	0	0
Gas-gangrene serum of maximum potency 1 cc/kg intravenously 3 hours after infection	4	3	0	0	0
Excision of wound 6 hours after infection gas-gangrene serum	8	3	0	0	0
	24	7	0	0	0
Excision of wound 3 hours after infection + gas-gangrene serum	8	8	4	4	4

Local treatment. with Marfanil powders immediately after infection (earth left in wound) and intravenous injection of gas gangrene serum.

	Number of animals	*Alive 24 hours after infection*	*Alive 8 days after infection*	*Alive 2 weeks after infection*	*Alive 3 weeks after infection*
MP powder N 982	6	6	6	6	
MP powder N 983	6	6	6	5	
MP powder 1:9	6	6	6	5	
MP powder P 55	6	6	6	6	
	24	24	24	22	21

Local treatment with Marfanil powders 3 hours after infection (earth left in wound) and intravenous injection of gas gangrene serum.

	Number of animals	*Alive 24 hours after infection*	*Alive 8 days after infection*	*Alive 2 weeks after infection*	*Alive 3 weeks after infection*
MP powder N 982	6	6	6	4	
MP powder N 983	6	6	6	6	
MP powder 1:9	6	6	4	2	
MP powder P 55	6	6	5	5	
	24	24	21	17	13

Local treatment with Marfanil powders 6 hours after infection (earth left in wound) and intravenous injection of gas gangrene serum.

	Number of animals	*Alive 24 hours after infection*	*Alive 8 days after infection*	*Alive 2 weeks after infection*	*Alive 3 weeks after infection*
MP powder N 982	6	6	4	4	
MP powder N 983	6	6	4	3	
MP powder 1:9	6	6	1	1	
MP powder P 55	6	6	1	1	
	24	24	10	9	7

Dosage (2 animals each): 0.5; 1.0; 1.5 g

This experiment on rabbits shows in a very impressive manner how vital the time factor is and how important it is to use the correct sulphonamides early in these serious wound infections. In this experiment Marfanil was combined with other sulphonamides in order also to produce a satisfactory effect on other microorganisms - such as streptococci and staphylococci - in the wound. The mixture in the ordinary MP powder was 1 part Marfanil to 9

parts Prontalbin : this was because large quantities of Marfanil were not available at first. Later the following MPE compounds, which were still more effective, were mainly used for local treatment of wounds :

Marfanil Prontalbin Eleudron	in equal parts (described in the experiment as MP powder N 982); or	Marfanil Prontosil rubrum Eleudron	in equal parts (described in the experiment as MP powder N 983)
Marfanil Prontalbin Eleudron Marfanil B	in equal parts	Marfanil Prontosil rubrum Eleudron Marfanil B	in equal parts

In the latter mixtures a readily soluble rapidly penetrating type of Marfanil was combined with a difficultly soluble Marfanil derivative which gave a still better local effect and which also had a considerable effect against tetanus infection. By using Marfnil B, the difficultly soluble naphthalene-1,5-disulphonic acid salt of 4-aminomethylbenzenesulphonamide, we succeeded in our experiments in preventing tetanus even in cases where, despite gas gangrene serum and tetanus serum, fatal tetanus otherwise occurred after 14 days. Marfanil B and powders containing Marfanil B are also recommended for use in the prevention of umbilical tetanus. The use of Marfanil powders on wound patients has given convincing results where they were administered in time. Anyone who has not treated a wound infected with gas gangrene by applying MPE powder externally within the first 3 hours and, where appropriate, by giving the patient large doses of Marfanil internally as well (if the wound is not easily accessible from outside), is bound to remain sceptical as to the value of sulphonamide treatment of wound infections. Processes which with other infections take days or even weeks take only hours with gas gangrene infections. Only swift action can help here.

In the light of experience to-date in the treatment of wounds, and especially those contaminated with earth, dust, etc., how should we proceed?

There is no question that all such wounds should first receive proper surgical treatment as quickly as possible. However, if there is no certainty that this can be done within the first three hours, as was often the case following air raids and always in the field, wounds should first be treated externally with Marfanil powder; up to 10 g, depending on the size of the wound, should be used in order to form a thin coating. If it is suspected that soil par-

titles or shell splinters, stones or wood fragments with soil clinging to them have entered the layers of tissue to such a depth that they are inaccessible to external treatment, then 2 g Marfanil, Marbadal, or Supronal should be given by mouth, preferably with a little gruel, milk, coffee, or the like. After surgical treatment of the wound, it should again be dusted with powder containing Marfanil; the total daily dose for adults should not exceed 20, or at most 25 g.

With wounds of very large area, such as were frequent as a result of severe burns suffered during air raids, it was found advisable not to apply more than about 10 g sulphonamide powder at once, since in such cases absorption is too rapid and symptoms of poisoning may appear. In order to prevent adhesion of dressings and to relieve pain, when the dressings are changed, during the first few days moist compresses with valerian tea or boiled water should be applied after the powdering, and then after a few days sterilized cotton cloths thinly smeared with ordinary ointment. This method is very economical from the point of view of consumption of ointment and is also more efficient than the use of sulphonamide ointments.

A dose of 10 g should likewise not be exceeded where MPE powders are being used in the abdominal cavity. That local treatment in cases of gunshot wounds in the abdomen has proved extremely efficient, is clear from the large series of observations made by Konjetzny and his pupils Haferland and Klostermeyer, as well as from the many observations made by Krueger and others.

Peipper, Tönnis and other specialists in the field of brain surgery have reported that even in cases of brain injury sulphonamides can be introduced directly into the wound cavities, thereby preventing abscess formation and meningitis, which are often fatal.

In Britain and America sulphonamides with additions of penicillin have been used, as well as pure sulphonamides, for the treatment of wound infections. Whether or not better results than with sulphonamides alone can be obtained in this way has not yet been reported.

Klostermeyer, who has had a very great deal of experience in the field with the correct and early application of sulphonamides, has told me that he cannot imagine better results than those obtained by him with this treatment. He draws particular attention to his results with severe wounds of the extremities, including the much dreaded wounds of the knee joint.

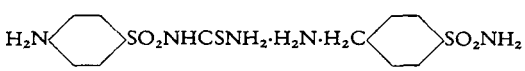
One further observation seems to me to merit special mention. In some of the great air raids all the severely wounded received suitable and prompt

surgical treatment and Marfanil. The results were correspondingly good. As the number of casualties was so great, however, it would have been impossible to give similar suitable surgical treatment to those with multiple minor injuries or even to incise the wounds and then treat them with Marfanil. These patients received no treatment, and the percentage of them who died was abnormally high, in contrast to that of the severely wounded (Hennig and others). The injuries were regarded as so trifling that no sulphonamides were administered, even internally. The wound infections which subsequently proved fatal could undoubtedly have been prevented in a great many cases by large oral doses of sulphonamides.

Whereas in World War I, the U.S. army lost 8.25% of its wounded by death, in World War II, when sulphonamides were used extensively, only 4.5% died. In World War I 1,68% of men reporting-sick in the American army died; now the figure is less than one tenth, i.e. 0.1% (Long, *J. Am. Med. Assoc.*, (1946)). The only reason why results of sulphonamide therapy of wound infections still vary so greatly from one section of the army to another is, in my view, that treatment is inadequate, and mostly too late. Even our experimental work showed dearly that better results can be achieved by correct chemotherapeutic treatment than by surgical treatment of wounds infected with gas gangrene, even when surgical attention is available 3 to 6 hours after the injury. In every case the best results were obtained by a combination of early and suitable surgical wound cleansing and sulphonamide treatment, preferably with the addition of gas gangrene serum. It goes without saying that even today the well-tried tetanus serum should never be dispensed with unless this is necessary for some special reason.

Sulphonamides will also come into general use in peace-time surgery. This is clear from the first publications of Konjetzny, Haferland, Klostermeyer, and others. W. Fischer of Kiel has reported that he used to have 13-14% fatal cases following operations for perforated appendix, but that since he has been using MPE powder, and with the same operating technique, the figure has fallen to 1%. Similarly favourable results have also been obtained by Lezius and Kramer, among others.

Marbadal-the Marfanil salt of sulphathiourea



for the synthesis of which we are also indebted to Klarer *(Deut. Med.*

Wochschr., No. 45-46 (1947) 670) - has an effect similar to that of Marfanil, but superior in the case of staphylococci.

In the case of *Clostridium septicum,* for instance, it has the following inhibiting values compared with other sulphonamides:

Prontalbin	<1:1000
Eleudron (Cibazol)	1:1000
Debenal (Pyrimal)	1:1000
Debenal M	1:1000
Marfanil	1:50,000
Marbadal	1:50,000
Debenal + Marbadal $\overline{aa}$	1:50,000
Debenal M + Marbadal $\overline{aa}$	1:50,000

In experiments on animals, too, Marbadal was at least as effective as Marfanil with anaerobes. *

Experiment 22.2.1946. Mice infected by intramuscular injections in the thigh with 0.3 cc of a 24-hour *Clostridium septicum* culture in liver broth diluted at the rate of 1 : 15 in a physiological solution of common salt. Doses, -administered to 2 animals in each case: 6% 0.2; 0.3 ; 0.5 ; 0.8 ; and 1.0 cc. A single-dose 1 hour after infection.

	Number of animals	*Alive 24 hours after infection*	*Alive 48 hours after infection*	*Alive 1 week after infection*	
Controls	20	8	3	2	
Marfanil 6% subcutaneous injection	10	10	9	8	18
6% by mouth	10	10	10	10	
Marbadal 6% subcutaneous injection	10	10	10	9	19
6% by mouth	10	10	10	10	

According to Lezius Marbadal is of outstanding value in the treatment of intestinal gangrene, also known as jejunitis necroticans, which has recently been claiming a great many victims in northern Germany. Schutz and Lezius were the first to establish that this disease is caused by pathogenic anaerobic bacteria. Whereas with surgical treatment 40-50% of patients died, Lezius

* Zeissler reports that Marbadal shows the same specific superiority over all other sulphonamides - even penicillin - when tested with *Bacillus enterotoxicus,* which over he considers to be the sole agent responsible for intestinal gangrene.

succeeded, by administering large doses of Marbadal by mouth, in saving the great majority of patients without operating.

Sulphonamides were first used for puerperal infections by Klee and his co-workers. Then in large-scale experiments British authors - first and foremost Colebrook and his co-workers - established for certain that Prontosil has a satisfactory action with puerperal infections. However, it was not only at a few very well-run clinics that convincing results were obtained; good results also gradually began to appear in the statistics from entire countries, such as Germany and Britain.

Further investigations conducted by us on puerperal infections, and especially in cases of septic abortion, showed that in a considerable percentage of cases anaerobic gas gangrene microorganisms were present, especially *Clostridium perfringens,* and sometimes also *Clostridium septicum, Clostridium novyi,* etc. According to Bernhard, Anselmino and others, the combination of Methyldebenal with Marbadal (De-Ma or Supronal), which our experimental investigations showed to be particularly advantageous and on which I reported in the *Deutsche Medizinische Wochenschrift,* 1947, *Nos.* 1-8, has also proved effective in these most serious forms of puerperal infections.

De-Ma and other sulphonamide combinations are better tolerated as well as being more effective. They result much less often in renal complications than do the pure sulphapyrimidines (cf. A. R. Frisk, G. Hagerman, S. Helander, B. Sjögren "Sulpha-Combination, a new chemotherapeutic principle", *Brit. Med. J.,* (1947) 7).

Martin and Lezius, among others, consider that with the protection of Supronal (= De-Ma) operations which used to be impossible can now be performed. Martin has reported cases of patients with fever due to a septic condition on whom a caesarean section was successfully performed with the use of De-Ma (Supronal).

Heilmeyer has reported on the successful treatment of very serious septic conditions with De-Ma in non-surgical medicine. Cholangitis also yielded to treatment. Even endocarditis lenta was cured in a few cases, one patient having suffered from the disease for 5 months. Hitherto only a temporary improvement could be brought about in patients with endocarditis lenta of longer standing. The failures are due not only to the anatomical reasons explained in earlier communications, but to some extent to the different strains of streptococcus responsible for the disease. Investigations conducted at the Heilmeyer Clinic have shown that strains classified as enterococci are particularly resistant. In our experiments on rabbits we found that some of these

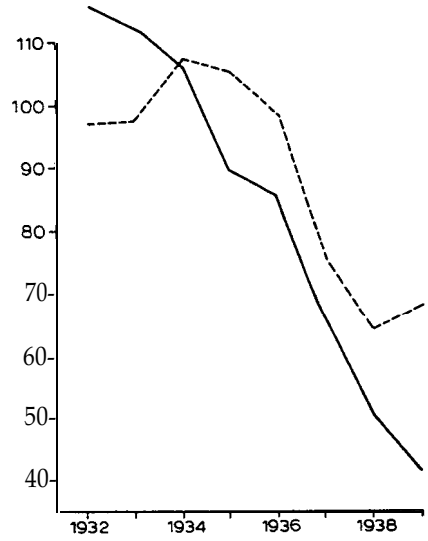


Fig. 1. Deaths from puerperal fever 1932-1939 following birth(.....) per 100,000 live and still births, and following miscarriages (--) per 1,000,000 of the average female population aged from 18 to less than 40 years.

strains caused very severe acute symptoms of the joints with swelling of the capsules and pericapsular haemorrhages. Some of them responded fairly well to Marbadal in infected mice. Still more effective sulphonamides will probably be found for these strains.

Mice infected by intraperitoneal injection of 0.3 cc of a 24-hour serum-broth culture diluted 1 : 8. Treatment 1, 6, 24, 48 and 72 hours after infection. Dose, administered to 2 animals in each case: 0.5% 0.5; 1.0 cc; 5% 0.2; 0.5; 1.0 cc per 20 g body weight by subcutaneous injection.

Penicillin 1 cc = 50 U. 0.5; 1.0 cc

I cc = 500 u. 0.2; 0.5; 1.0 cc

Some of the strains isolated in cases of endocarditis lenta also proved to be completely resistant to penicillin. Christie reported very considerable successes with some patients suffering from endocarditis lenta who were given large doses of penicillin. A combination of the two best drugs at present available against streptococcal infections - penicillin and the sulphapyrimidine compounds or De-Ma - may perhaps give even rather better results than those which have hitherto been possible under the most favourable conditions.

	Number of animals	*Alive 24 hours after infection*	*Alive 48 hours after infection*	*Alive 1 week after infection*
Controls	20	2	1	0
Prontalbin	10	7	4	0
Sulphathiazole	10	4	3	1
Debenal	10	5	2	1
Debenal M	10	2	1	1
Marbadal	10	7	7	4
De-Ma (Supronal)	10	6	5	4
Debenal/Marfanil āā	10	8	7	7
Debenal M/Marfanil āā	10	10	10	8
Penicillin	10	10	9	8

With less serious streptococcal infections, such as erysipelas, quinsy, tonsillitis, etc., the older sulphonamides are reliable and effective. We now know for certain that the sulphonamides are of decisive value in the treatment of erysipelas, especially as even erysipelas in infants, where the mortality used to be almost 100%, can now be cured by means of sulphonamides in the vast majority of cases. The ordinary sulphonamides are also still being used for the treatment of severe quinsy and tonsillitis, the most efficient method being to allow the tablets to dissolve very slowly in the mouth so that they act for the maximum length of time and with the maximum intensity directly upon the focus of infection. W. Schmidt therefore even went so far as to recommend that sulphonamides should be applied only locally for quinsy and tonsillitis; he dusted several times a day with MP powder and obtained very good results. Moreover, local application of Marfanil together with serum should also be used in every serious case of diphtheria since, of all the sulphonamides, Marfanil develops the most powerful inhibiting effect on diphtheria bacilli, thereby limiting further toxin production and at the same time fighting infection by associated bacteria.

In severe cases of streptococcal meningitis Unterberger reduced the 80% mortality at first to 50%, later - with Tibatin - to 25% and finally to as little as 11%.

In the treatment of lobar pneumonia little has changed since the introduction of sulphapyridine. It may be possible to improve slightly on the results so far achieved with sulphapyridine and sulphathiazole by using the newer sulphonamides, especially sulphapyrimidines and Supronal. British authors, with their greater experience of penicillin, consider that in cases of lobar pneumonia the results achieved with the sulphonamides are so good that the

question ofpenicillin scarcely arises. Here again, as far as the use of both these drugs is concerned, everything depends on when they are applied. According to Bunn and co-workers *(J. Am. Med. Assoc.,* 129, No. 5 (1945)), if penicillin is to be administered by mouth for the treatment of pneumonia the dose must be 4-5 times greater than with intramuscular injection, or 750,000 units on the first day and 400,000-500,000 U. on the following days. Treatment should be considered for at least 7 days following return to normal temperature. It appears that penicillin is more effective than the sulphonamides against other pneumococcal infections.

Results with bronchopneumonia are still not as good as with lobar pneumonia. This is undoubtedly due in part to the fact that bronchopneumonia begins less dramatically than lobar pneumonia and is therefore never treated so intensively. Apart from this, it appears that in some areas there are forms of pneumonia, caused by enterococci, which when treated with sulphonamides have a non-typical course. Non-typical virus pneumonia has so far not been reliably identified in Germany to any extent worth mentioning.

Among the sulphonamides the most effective against staphylococcal infections are sulphathiazole (Eleudron, Cibazol), Globucid, and Marbadal. External application of MPE powders, where possible as an embrocation with glycerin or in the form of a lotion consisting of:

Zinc oxide
Talcum
Glycerin } in equal parts
Water
5% MPE

has proved particularly successful.

This treatment has been found practical, and economical with regard to dressings.

One would expect penicillin to give better results than the sulphonamides against staphylococci in practice, as it is so very effective in vitro.

One of the most brilliant successes with sulphonamides has been against meningitis epidemica - a disease which formerly resulted in a high percentage of deaths. In some epidemics the death rate used to be 80-90%, and even approx. 50% after the use of serum. Now, results published in the literature throughout the world show that 90-95% of patients suffering from meningitis epidemica are saved by oral administration of sulphonamides alone. In a recent communication Gehrt states that he has even been able to reduce the mortality among babies and small children, who are least able to withstand

this disease, to 4.8%. In the U.S. army the number of fatal cases among soldiers suffering from meningitis epidemica fell from 39.2% in World War I to 3% in World War II thanks to the use of sulphonamides. Even according to reports dating from some time back the lives of more than 10,000 persons suffering from meningitis epidemica had already been saved by sulphonamides in Britain alone.

In bacillary dysentery and related infections sulphanilamide (Prontalbin), sulphathiazole (Eleudron, Cibazol), sulphapyrimidine (Debenal, Pyrimal, Sulphadiazine), and sulphaguanidine are of particular value. According to Max Bürger the sulphonamides have not only removed the danger of dysentery as far as the individual is concerned but have also removed the danger of dysentery as an epidemic disease. Penicillin is ineffective against dysentery bacilli. American authors report that the sulphapyrimidine compounds are most effective here.

Results with the sulphonamides in typhoid and paratyphoid fever have so far been unsatisfactory. According to experimental results (given below) obtained with sulphapyrimidine compounds (Debenal, Debenal M) in paratyphoid B infections we can perhaps also look for some success in practice.

The effects of sulphonamides on paratyphoid B infection are illustrated by the following experiments:

Mice infected by intraperitoneal injection with 0.5 cc of a 24-hour broth culture diluted 1 : 50. One subcutaneous or intramuscular injection 1 hour after infection, 2 animals in each case, all preparations 2% 0.2; 0.3; 0.5; 0.8; and 1.0 cc.

		Number of animals	*Alive 48 hours after infection*	*Alive 1 week after infection*	*Alive 2 weeks after infection*
Controls		20	10	5	
Debenal	subcutaneous injection	10	9	8	7
	intramuscular injection	10	10 } 19	10 } 18	8 } 15
Debenal M	subcutaneous injection	10	9	9	6
	intramuscular injection	10	9 } 18	9 } 18	8 } 14
De-Ma	subcutaneous injection	10	10	10	6
	intramuscular injection	10	10 } 20	9 } 19	6 } 12

With still more. intense infection and 3 corresponding injections after 1, 6, and 24 hours the following result was obtained.

		Number of animals	*Alive 48 hours after infection*	*Alive 1 week after infection*	*Alive 2 weeks after infection*
Controls		20	3	1	1
Debenal	subcutaneous injection	10	7 } 15	5 } 10	2 } 4
	intramuscular injection	10	8 }	5 }	2 }
Debenal M	subcutaneous injection	10	6 } 13	2 } 5	2 } 3
	intramuscular injection	10	7 }	3 }	1 }
De-Ma	subcutaneous injection	10	9 } 18	6 } 11	1 } 6
	intramuscular injection	10	9 }	5 }	5 }

De-Ma in solution was to some extent even more effective.

Experiment 2.3.1947. Mice infected intraperitoneally with 0.5 cc of a 24-hour broth culture diluted 1 : 20. Animals, 2 in each case, treated 3 times with 2% 0.1; 0.2; 0.3; 0.4; 0.5; by intravenous injection; and 0.2; 0.3; 0.5; 0.8; 1.0; by subcutaneous injection and by mouth.

		Number of animals	*Alive 48 hours after infection*	*Alive 2 weeks after infection*
Controls		20	11	2
De-Ma soluble	intravenous injection	10	7	5
	subcutaneous injection	10	9 } 26	8 } 22
	by mouth	10	10	9
Debenal in aqueous suspension	2% subcutaneous injection	10	10 } 20	7 } 15
	2% by mouth	10	10	8 }
Debenal M	2% subcutaneous injection	10	10 } 20	7 } 14
	2% by mouth	10	10	7 }

With coli infections it is much more difficult to arrive at a definite assessment of the effect; this is because, even with the controls, the course of the infection is often irregular. Nevertheless, such an assessment can be made if experiments are constantly repeated with different culture dilutions. The following experiment, in which culture dilutions of 1 : 3 and 1 : 5 were used for infecting the animals, gives some information on the effectiveness of Debenal and De-Ma. Dose 5%, 2 animals in each case, subcutaneous injection and by mouth 0.2; 0.5; 1.0 cc.

		Number of animals	*Alive 24 hours after infection*	*Alive 48 hours after infection*	*Alive 1 week after infection*
Controls:					
Culture dilution 1:3		12	5	2	0
Debenal	subcutaneous injection	6	1	1	1
	by mouth	6	4 } 5	3 } 4	2 } 3
De-Ma	subcutaneous injection	6	4	4	4
	by mouth	6	6 } 10	5 } 9	5 } 9
Controls:					
Culture dilution 1:5		12	9	7	5
Debenal	subcutaneous injection	6	5	3	2
	by mouth	6	6 } 11	6 } 9	5 } 7
De-Ma	subcutaneous injection	6	6	6	5
	by mouth	6	6 } 12	6 } 12	4 } 9

In this context it is not possible to go into any great detail on the use of sulphonamides against many other infections, such as undulant fever, actinomycosis, etc.

With undulant fever definite results are obtained only after prolonged treatment.

Rats infected by intraperitoneal injection with 0.5 cc of a 48-hour agar-broth slope. One injection 1 hour after infection, then daily for 14 days, 2 animals in each case, 5% 0.2; 0.5; 1.0; 2.0 cc.

	Number of animals	*Alive 48 hours after infection*	*Alive 1 week after infection*	*Alive 2 weeks after infection*
Controls	8	5	0	0
Prontalbin 5% subcutaneous injection	8	7	5	3
Tibatin 5% subcutaneous injection	8	8	7	6
Debenal M 5% subcutaneous injection	8	8	7	6

I should also like to draw attention to a recent report by Klee that Tibatin has proved particularly satisfactory in the treatment of lung gangrene.

Information on the use of sulphonamides in relatively rare diseases is given in Domagk-Hegler*: Chemotherapie bakterieller Infektionen* (Chemotherapy of bacterial infections), 3rd ed., Hirzel, Leipzig, 1944, and Domagk: *Pathologische Anatomic und Chemotherapie bakterieller Infektionen* (Pathological anatomy and chemotherapy of bacterial infections), Thieme, Stuttgart. Information on the innumerable other sulphonamides which have been tested and used is given in Mietzsch's survey: "Therapeutisch verwendbare Sulfonamid- und Sulfonverbindungen" (Therapeutically useful sulphonamide and sulphone compounds), Suppl. 54 (1945) to "Chemiea", *Z. Ver. Deut. Chemiker.*

A fourth phase in chemotherapy of bacterial infections seems to be opening up in view of the fact that the sulphathiazole and sulphathiodiazole compounds have had such a specific action against tubercle bacilli that further progress at last seems possible in this direction too. In 1940 I reported the observation that sulphathiazole in concentrations of 1 : 5000 has a specific inhibiting action on tubercle bacilli, whilst other sulphonamides and sulphones, as well as Diasone and Promin (which are frequently referred to in the literature), do not. Only the thiazole and thiodiazole derivatives have this effect. Further experiments showed that these sulphonamides have this specific effect against the human as well as the bovine and avian types - temporarily in concentrations as low as 1 : 50,000 or even 1 : 100,000, i.e. sulphonamide concentrations which can easily be achieved in the human organism, and with very small doses at that.

Even at that time I suggested that sulphathiazole and its derivatives might be effective against human disease, but since then further results have shown me that an effect can be achieved with even smaller doses than were then being recommended, provided that these small doses are given for weeks and perhaps months on end. Experiments have shown that it is best to begin treatment with small doses, especially where many bacilli are present and where treatment is to be continued for a considerable period. Otherwise, as a result of the damage suffered by the tubercle bacilli and of their accelerated decomposition, too many toxins are liberated and in consequence undesirable abscess formations and sequestrations as well as general detrimental effects are liable to occur, as after the administration of tuberculin. It was in fact found from long-term experiments on animals that the largest doses were by no means always the most effective. In critical cases in man the risk at-

tendant upon very high doses would of course have to be accepted. In cases of meningitis tuberculosa there should probably be no hesitation in giving high doses. Where the patient's life is not in danger, however, minimal doses, 1 x 0.25 g or 2 x 0.25 g daily, should be administered at first; then, after 2-3 weeks, 3 x 0.25 or 4 x 0.25 g daily, but the doses should never be increased until the patient feels better.

My colleagues in chemistry Dr. Behnisch, Prof. Schmidt and Dr. Mietzsch and I finally arrived at still more effective compounds which were no longer sulphonamides at all - for, as I have shown, the specific effect had up to that time been detectable only with the sulphonamide compounds of the thiazole and thiodiazole series. It was Behnisch who made available to me for chemo-

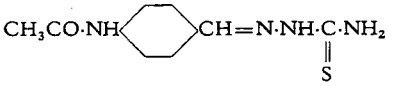
Fig. 2. Inhibiting effect of sulphathiazole on human-type tubercle bacilli from sputum Fr. Di.

Tube 1 (control with good growth, 6 weeks after inoculation)
Tube 2 contains 1: 5,000 sulphathiazole
Tube 3 contains 1: 10,000 sulphathiazole
Tube 4 contains 1: 25,000 sulphathiazole
Tube 5 contains 1: 50,000 sulphathiazole
Tube 6 contains 1: 100,000 sulphathiazole

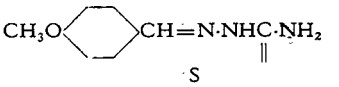
In this experiment no cultures of tubercle bacilli were visible in any of the tubes containing sulphathiazole, 6 weeks after inoculation.

therapeutical trials the first thiosemicarbazones of cyclic aldehydes, which he was using as initial products in the manufacture of sulphathiodiazoles and which represent the open-ring preliminary stage in the 2-aminothiodiazoles necessary for this. The thiosemicarbazones of cyclic aldehydes and ketones showed a powerful inhibiting action on tubercle bacilli. In this way a new chemotherapeutical principle, which is not dependent on the presence of the sulphonamide group, was extracted from the principle of the sulphathiazoles and sulphathiodiazoles. In the light of experiments the thiosemicarbazones even appear in some respects to have advantages over the sulphathiazoles and sulphathiodiazoles. Thus, their effectiveness against the various types of tubercle bacillus is not reduced by para-aminobenzoic acid, protein breakdown products, Campolon or other substances which, as already shown, can considerably impair the effectiveness of sulphathiazole and of the sulphathiodiazoles. Tuberculin is not one of the substances which impair the effectiveness against tubercle bacilli of those sulphonamides which in themselves are effective. In animal experiments the effectiveness of compounds containing no sulphonamides was for the most part even clearer than with the above-mentioned active sulphonamides of the thiazole and thiodiazole series. This new class of active substances was first reported in a joint publication by R. Behnisch, F. Mietzsch, H. Schmidt and myself in *Naturwiss., 33, No.* 10 (1946). The following compounds proved to be very effective :

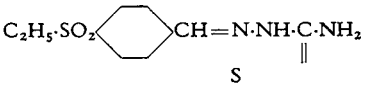
Tb I/698 =

Schmidt (Sdt) 1041 

Tb II/242 =

Schmidt (Sdt) 1075 

Tb III/1374 =

Behnisch (Be) 1374 

whereas *Tb IV* is a thiodiazole compound which is sensitive to *p*-aminobenzoic acid.

Experiment with human type, inoculation on 24th April; first collection (I) on 8th May, 1947; second collection (II) on 14th May.

	1:5000		1:10,000		1:25,000	
	I	*II*	*I*	*II*	*I*	*II*
Eleudron-Na	o	o	o	o	o	o
TbI/698	o	o	o	o	o	o
Eleudron/Tb I $\overline{aa}$*	o	o	o	o	o	o
Tb II/242	o	o	o	o	o	o
Eleudron Tb II $\overline{aa}$	o	o	o	o	o	+
Tb III/1374	o	o	o	o	o	o
Eleudron/Tb III $\overline{aa}$	o	o	o	o	o	o
Tb IV	o	o	o	o	o	o
Eleudron/Tb IV $\overline{aa}$	o	o	o	o	o	+
Badional	+	+	+	+	++	+++
Sulphapyridine	++	+++	++	+++	++	+++
Prontalbin	++	+++	++	+++	++	+++

* Eleudron and Tb I/698 mixed in equal parts.

Controls: First collection (I) after 14 days: ++/+++
Second collection (II) after 3 weeks: +++

(o = no growth; ++ = pronounced growth, but no spore formation; +++ = intense growth.)

The same experiment but with *p*-aminobenzoic acid added to the nutrient medium at the rate of 1:10,000.

	1:5000		1:10,000		1:25,000	
	I	*II*	*I*	*II*	*I*	*II*
Eleudron-Na	o	o	o	+	++	+++
Tb I/698	o	o	o	o	o	o
Eleudron/Tb I $\overline{aa}$	o	o	o	o	o	o
Tb II/242	o	o	o	o	o	o
Eleudron/Tb II $\overline{aa}$	o	o	o	o	o	++
Tb III/1374	o	o	o	o	o	+
Eleudron/Tb III $\overline{aa}$	o	o	o	o	+	+
Tb IV	o	o	o	o	++	+++
Eleudron/Tb IV $\overline{aa}$	++	+++	++	+++	++	+++
Badional	++	+++	++	+++	++	+++
Sulphapyridine	++	+++	++	+++	++	+++
Prontalbin	++	+++	++	+++	++	+++

Controls: First collection (I) after 14 days: ++/+++
Second collection (II) after 3 weeks: +++

Experiment with bovine type.

	1:5000		1:10,000		1:25,000	
	I	*II*	*I*	*II*	*I*	*II*
Eleudron-Na	o	o	o	o	o	o
Tb I/698	o	o	o	o	o	o
Eleudron/Tb I $\overline{aa}$	o	o	o	o	o	o
Tb II/242	o	o	o	o	o	o
Eleudron/Tb II $\overline{aa}$	o	o	o	o	o	+
Tb III/1374	o	o	o	o	o	o
Eleudron/Tb III $\overline{aa}$	o	o	o	o	o	o
Tb IV	o	o	o	o	o	o
Eleudron/Tb IV $\overline{aa}$	o	o	o	o	o	+
Badional	+	+	++	++	++	++/+++
Sulphapyridine	(+)	+	++	++/+++	++	++/+++
Prontalbin	+	++/+++		++/+++	++	++/+++

Controls: First collection (I) after 14 days: +/++
Second collection (II) after 3 weeks: ++/+++

Same experiment with bovine type, but with para-aminobenzoic acid added to the nutrient medium at the rate of 1:10,000.

	1:5000		1:10,000		1:25,000	
	I	*II*	*I*	*II*	*I*	*II*
Eleudron-Na	o	o	o	o	o	++
Tb I/698	o	o	o	o	o	o
Eleudron/Tb I $\overline{aa}$	o	o	o	o	o	o
Tb II/242	o	o	o	o	o	o
Eleudron/Tb II $\overline{aa}$	o	o	o	o	o	+
Tb III/1374	o	o	o	o	o	+
Eleudron/Tb III $\overline{aa}$	o	o	o	o	o	+
Tb IV	o	o	o	o	+	++
Eleudron/Tb IV $\overline{aa}$	+	++	+	++	+	++
Badional	+	++	+	++	+	++/+++
Sulphapyridine	++	++/+++	++	++/+++	++	++/+++
Prontalbin	+	++/+++	+	++/+++	+	++/+++

Controls: First collection (I) after 14 days: ++/+++
Second collection (II) after 3 weeks: +++

Like *p*-aminobenzoic acid, liver extracts, e.g. Campolon, and other proteolytic products develop an antisulphonamide action with regard to tubercle bacilli. Koch's original old tuberculin did not show this effect in the concentrations tested (1:100).

In some cases in experimental animals which had only received 1 local application it was possible to detect some effect from the drugs and to differentiate between them.

Guinea-pigs were infected in the back with an intramuscular injection of 3 mg of a human type culture. After 3 days the infection site was incised and 0.5 g of the preparation was applied locally. In the controls extensive caseating foci had already appeared after 4 weeks in the area of the injection site on the back. In the internal organs - mainly lung, liver, spleen - nodules and sometimes necrotic areas could be seen under the microscope and usually with the naked eye. Eight weeks after being infected none of the control animals was alive. In the case of the animals which were treated locally with Tb 1, after 4 weeks small fusion foci only, with increased reaction of the connective tissue in the surrounding area, were apparent in the musculature; in addition, in the area round these foci the experimental animals, in contrast to the controls, showed only isolated and non-typical epitheloid nodules. In some of the animals which were treated locally with Tb I/698 there was no fusion whatever at the infection focus but only a proliferation of connective tissue with individual histocytes, though without epitheloid nodules. Another

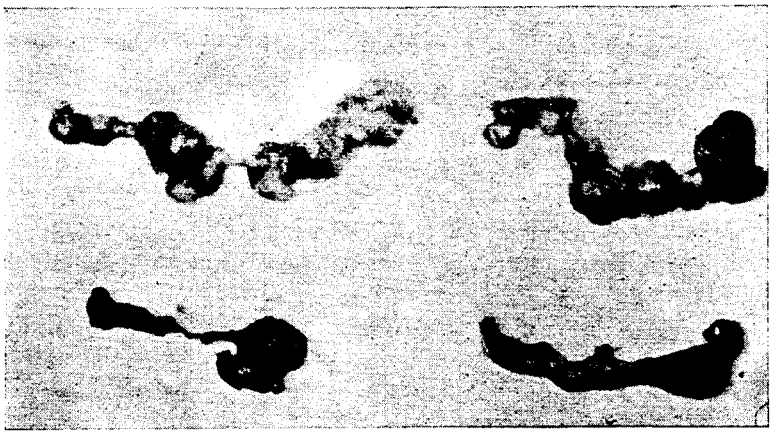


Fig. 3. Guinea-pigs infected intraperitoneally with human type tubercle bacillus
(Above): Controls. Large tuberculous foci in the omentum.
(Below): The same infection as above with animals treated with Tb I/698. Small tuberculous foci only.

striking fact was that only very isolated small nodules could be found in the lung, liver or spleen, whereas in the untreated controls there were comparatively extensive tuberculous changes. Evidence of inhibition of tuberculous tissue changes was also to be found in the animals treated with Tb II and Tb III, but was not so pronounced as with Tb I. In the animals treated with Tb IV the disintegrated reticular epitheloid nodules around the local necrotic areas of the primary focus were very noticeable. In the animals which received one local treatment with Eleudron the effect was still less than with Tb IV. All the animals showed numerous epitheloid nodules in lungs, liver and spleen, although in some cases with non-typical disintegration.

With animals infected by intraperitoneal injections of large doses of tubercle bacilli the caseation processes appeared mainly in the omentum, but subsequently also in the spleen, liver and lung. These latter organs showed caseation as well as productive foci, depending on the quantities of tubercle bacilli injected. In the treated animals the caseated foci remained smaller, and in some cases processes (mainly productive) appeared which, if treatment was continued for a sufficiently long period, changed into unspecific granulation scar tissue.

In the treatment of experimental animals substances of this kind with a highly effective specific action against tubercle bacilli gave the following results :

1. A local effect with powder applied locally.
2. When administrered by mouth and by subcutaneous injection, in cases of intraperitoneal infection in the omentum and elsewhere a general effect on tuberculous processes at some distance from the site of application.
3. Absence or delay of generalization.

Histologically the treated animals-unlike the heavily infected untreated controls, in which caseation was present - showed:

1. Leucocytic inflammation. Caseous disintegration of the leucocytes clearly retarded.
2. Considerable numbers of histocytes with accumulation of Indian ink, where Indian ink had been added to the tubercle bacilli at the time of infection.
3. Non-typical nodules.
4. Non-typical giant cells.
5. Completely unspecific granulation tissue.

The nature of the histological tissue reaction appears to be entirely inde-

pendent of the immunity or resistance, and to be dependent only on the number of bacilli capable of developing when exposed to the effects of the drug. Thus, depending on the degree of success, we see relatively slight caseation in the treated animals, more proliferative processes with occurrence of non-typical cells, and finally unspecific granulation tissue formation. In experiments where only few bacilli are used for infection and where primary caseating processes do not occur, the specific productive foci appearing in the controls sometimes turn into wholly non-typical histocytic foci and finally into completely unspecific granulation and scar tissue. In the animals treated with the optimum doses no tuberculous foci whatever develop in the other organs, whilst with sub-optimum doses the development of these foci is inhibited. Unlike the controls, the animals in which the seat of the primary infection was the vestibule of the eye showed caseous-fusion. Even when, in heavily infected animals, destruction occurred owing to the effect of the toxin, unspecific granulation tissue foci covered with epithelium also developed here at a later stage in the treated animals. In contrast to the untreated controls, in which numerous epithelial nodules appeared in the spleen, liver and lung, the treated animals showed no tuberculous foci in these organs, either upon visual inspection or under the microscope. With rabbits, among which the controls showed tuberculous changes in the lungs, kidneys and other organs, it was likewise possible to prevent the development of tuberculous processes by means of long-term treatment with the active substances. It remains to be seen whether or not the substances which were found to be effective against tuberculosis in the experiment will be sufficiently effective in clinical practice.

The effectiveness of the substance Tb I/698 in the case of tuberculosis of the skin in man has been confirmed. Moncorps and Kalkoff have reported on this. The successes with lupus of the skin reported by Moncorps and Kalkoff for the first time at the 1947 Rhine-Westphalian Dermatology Conference have since been corroborated by Grütz, P. Schmidt, Koch, Hartung and others. Eickhoff of the Loebell Clinic for Ear, Nose and Throat Diseases in Münster, Westphalia, reported on the effectiveness of the preparation Tb I/698 in cases of lupus of the mucous membranes at the Congress of Ear, Nose and Throat Specialists in Hamburg on 7th and 8th November, 1947. He described clinical and histological cures of patients who had been treated for years in hospital without success. Average length of treatment to-date: 110 days with a dose of 1 g per day.

In the light of results of resistance tests on tubercle bacilli from sputum I

have reason to assume that there are also tubercle bacilli with differing degrees of resistance to sulphathiazole and other substances which appear suited to chemotherapy of tuberculosis. However, if we were able to devise a method of chemotherapy of tuberculosis in man on the basis of the experimental findings so far available, even this measure might result in failure unless from the outset we took the utmost care to ensure that patients with overt tuberculosis who were spreading the bacilli were isolated until completely cured. Otherwise, even with the very best drugs against tuberculosis we should perhaps see the same result as we are now beginning to see in the treatment of gonorrhoea with sulphonamides and penicillin - drugs with which, if the correct procedure had been adopted, gonorrhoea could no doubt have been eradicated.

By far the greatest danger threatening us at the present time is pulmonary tuberculosis, especially where large parts of Europe have been turned into famine areas, for this disease will not stop at the boundaries of the stricken areas of central Europe. Whether chemotherapy of tuberculosis, which is only in its infancy, has yet reached the stage of being really effective here is a question which cannot be answered until further investigations have been carried out by many experienced clinicians on the strictest scientific lines. At a meeting of the Flensburg Medical Association in November 1949 F. Kuhlmann reported for the first time favourable results in patients seriously ill with pulmonary tuberculosis. The successes took the form of disappearance of the fever (some of the patients having suffered from very prolonged high fever), diminution of sputum and sometimes disappearance of bacilli from the sputum, a return to normal in blood sedimentation and gains in weight. Kuhlmann reported that the patients themselves asked for the treatment and that the mortality rate in the department for patients seriously ill with pulmonary tuberculosis fell from 7-8% to 1-2% per month with approx. 160 beds occupied. He pointed out that with the fall in the mortality curve the type of case accommodated in the department changed somewhat because sanatorium patients were temporarily admitted (60), but that only patients selected for the seriousness of their condition were transferred there. He also allowed for the fact that the hot dry summer might have had a beneficial effect, but considered that the possibility that hospitalization itself had some effect could be ruled out in the case of the large majority of patients. X-ray photographs showed that in many of the patients who had received treatment there was extensive resorption of the exudative changes. Ausculation lagged behind radiography in detecting a decrease in the infection. Accord-

ing to Kuhlmann, in the patients who received treatment there was a surprising change in the course of the disease. Nevertheless, it would be too early to speak of a cure, although Kuhlmann said that in some cases the word "cure" suggested itself. We shall therefore have to wait and see whether in these cases the cure is definite and whether the successes reported by Kuhlmann can be regularly repeated with the same treatment. However, it would appear that for the first time we are in possession of substances which bring chemotherapy of pulmonary tuberculosis within striking distance. Many lines of inquiry were pursued before we reached this goal. The least hint that a substance might be effective was recorded and followed up by the chemists who, on the strength of it, made innumerable syntheses. And how often in vain! Chemotherapy of tuberculosis in its present state is also a late fruit of sulphonamide research, for which the foundations were laid in my joint work with Klarer and Mietzsch. Which cases of tuberculosis should receive chemotherapeutic treatment, is a question which is constantly being asked, and in reply I would refer to an axiom which I often quote: I consider it my first duty in the development of chemotherapy to cure those diseases which have hitherto been incurable, so that in the first place those patients are helped who can be helped in no other way.

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