6 ON THE THERAPY OF PULMONARY ASPERGILLOSIS WITH A NEW ORAL ANTIMYCOTIC BAY-b 5097

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At the 10th Congress of the Japanese Chest Diseases Society, July 13th, 14th, 1970, in Sendai, Japan, we reported the results of a survey done in all in-patients of this hospital for Asp. fumigatus infections. This survey conducted in January 1969 included sputum cultures, Asp. fumigatus complement fixation tests and clinical diagnostics. Measures approximately 25% of the patients examined yielded positive results for Aspergillus.

Table 1 shows findings of the check-up for pulmonary mycotic infections conducted for all in-patients of Tomakomai Hospital.

During the study, the significance of the complement fixation tests for diagnosis and evaluation of therapy was appreciated.

We also pointed out the difficulties to achieve satisfactory therapeutic results with presently known drugs and methods. Combinations of inhalation of Amphotericin B and orally Nystatin has been our routine.

Table 2 shows results of patients treated previously with Amphotericin B and Nystatin. Since results were not satisfactory in all cases, 9 out of 18 patients were put on Bay-b 5097 regimen.

We were given the opportunity to use clinically a new antimycotic substance Bay-b 5907 developed by Farbenfabriken Bayer AG, West Germany, with Bis-phenyl-(2-chlor-phenyl)-1-imidazolylmethane. It's generic name is Clotrimazol. It acts primarily fungistatic, but has wide spectrum fungicidal effects when surum levels of over 20 gamma/ml are reached. Bay-b 5097 is available in gastric soluble capsules and in tablet form each containing 500 mg of active substance.

Clotrimazol being insoluble in water had to be dissolved in a proper medium to prepare a standard stock solution for *in vitro* tests and we choose propyleneglycol for that. By the hydrophilic oily solvent method the substance was dissolved completely to make a stock solution. Then this suspension was diluted down to the desired gamma levels. Since the stock solution shows a certain instability due to hydrolysis care should be taken to use the suspension only in its stable state. IFO-4057 Asp. fumigatus supplied by the Medical Science Research Institute of Tokyo University and the Institute of Fermentation Research Osaka were used as standard test strains. Using the a.m. standard stock solution and test strains, taking into considerations the hydrolysis, with the vertical diffusion method prescribed by the Japanese Ministry of Health and Welfare, the zones of inhibition were measured to establish a standard gamma curve. A clear inhibitory zone was observed at 1.0 gamma in Sabouraud culture medium. The minimum effective concentration of Bay-b 5097 was found to be 0.3 gamma when diluted in water and 0.5 gamma in Sabouraud liquid culture medium. The minimum concentration of Bay-b 5097 for preventing germination was assessed at 0.2-0.3 gamma.

Table 1. Results of Sputum Examination for Fungus and Aspergillus fumigatus Complement Fixation Test

Case	Age	Sex	Respiratory Symptoms	Tbc. Bac.	Identification	Asp. fumig. C-F. Test	Lesion	Comments
U.K.	33	F	(±) Hemoptysis	(−)	Asp. fumigatus	X 128	Bronchus	Rt. Paraffin Plombage, 1968
M.S.	40	F	(+) Hemoptysis	(−)	Asp. fumigatus	X 128	Bronchus	Bilat. Paraffin Plombage, 1968
I.S.	54	M	(±)	(+)	Asp. fumigatus	X 32	Broncho-pulmonary	
F.S.	42	M	(++) Hemoptysis	(−)	Asp. fumigatus	X 16	Bronchus (cavity+)	
S.H.	64	M	(±)	(−)	Asp. fumigatus	X 16	Bronchus	Lt. Paraffin Plombage, 1968
E.K.	31	F	(−)	(−)	(−)	X 128	Bronchial Stump (?)	Lt. Upper Lobectomy, 1968
S.Y.	51	M	(+)	(+)	(−)	X 32	Bronchus (cavity+)	
H.S.	72	M	(±)	(−)	(−)	X 32	Bronchus	
S.N.	66	F	(−)	(−)	(−)	X 32	Bronchus	
M.T.	66	F	(+)	(−)	(−)	X 32	Bronchus (cavity+)	
S.Y.	17	F	(−)	(−)	(−)	X 8	Bronchus	
S.I.	44	F	(±)	(−)	(−)	X 8	Bronchial Stump (?)	Lt. Upper Lobectomy, 1968
H.N.	67	M	(±)	(−)	(−)	X 8	Bronchus (cavity+)	
I.Y.	78	M	(++) Hemoptysis	(+)	(−)	X 8	Bronchus (cavity+)	
Y.R.	95	M	(±)	(+)	(−)	X 8	Bronchus (cavity+)	
K.N.	36	M	(±)	(−)	(−)	X 8	Bronchus (cavity+)	
Y.I.	72	M	(±)	(+)	(−)	X 8	Broncho-pulmonary	
K.K.	44	F	(+) Hemoptysis	(−)	(−)	X 8	Bronchus (cavity+)	Dermatomycosis (Asp. niger)
S.Y.	44	M	(±)	(−)	Asp. fumig-series	(−)	Pyothorax	
W.J.	71	M	(++)	(+)	Asp. fumig-series	(−)	Broncho-pulmonary	
N.I.	80	M	(++)	(−)	Asp. fumig-series	(−)	Bronchus	Bronchial Asthma
I.C.	56	M	(++) Hemoptysis	(+)	Asp. fumig-series	(−)	Bronchus	Lung Protozoa
M.I.	36	M	(±)	(+)	Asp. fumig-series	(−)	Bronchus (cavity+)	
I.K.	23	M	(+)	(−)	Asp. fumig-series	(−)	Bronchus (cavity+)	
M.K.	69	M	(−)	(−)	Asp. fumig-series	(−)	Bronchus	
N.N.	74	M	(−)	(−)	Asp. fumig-series	(−)	Bronchus	
S.E.	51	M	(+)	(+)	Asp. fumig-series	(−)	Bronchus (cavity+)	
K.S.	29	F	(−)	(−)	Asp. fumig-series	(−)	Aspergillom	
K.G.	34	F	(−)	(−)	Asp. fumig-series	(−)	Bronchial Stump (?)	Lt. Pneumonectomy 1960
M.F.	59	F	(+)	(+)	Asp. fumig-series	(−)	Bronchus (cavity+)	
T.T.	25	F	(−)	(−)	Asp. fumig-series	(−)	Bronchus	
K.T.	31	F	(+)	(+)	Asp. fumig-series	(−)	Bronchus (cavity+)	
S.H.	41	F	(++) Hemoptysis	(+)	Asp. fumig-series	(−)	Bronchus (cavity+)	Diabetes Mellitus
W.F.	26	M	(−)	(−)	Asp. fischeri-series	(−)	Bronchial Stump (?)	Rt. Segmentectomy (S_6)
K.Y.	22	M	(−)	(−)	Asp. fischeri-series	(−)	Bronchus	
Y.A.	28	M	(+) Hemoptysis	(−)	Asp. fischeri-series	(−)	Bronchus	Rt. Paraffin Plombage, 1968
Y.N.	55	M	(±)	(−)	Asp. ustus (−)	(−)	Bronchus (cavity+)	

(January, 1969)

Table 2. Clinical Cases Treated with Amphotericin B (Inhalation) and Nystatin (Medication)

	No.	Cases	Age	Sex	Respiratory Symptoms	Lesion	Identification	Days Treated	Effect Resp.	Effect Sympt.	Effect Colonies	Asp. fumig. C-F Test Pre Med.		Asp. fumig. C-F Test Post Med.		Clinical Course	Comments
Primary	2	F.S.	60	M	(−)	Aspergillom	Asp. fumigatus	28			(−)	X	36	(−)		Completely Cured	Rt. Upper Lobectomy
	3	Y.E.	26	M	(−) Hemoptysis	Bronchus	Asp. fumigatus	75	(−)		(−)	X	18	(−)		Completely Cured	Amph. B 10 mg I.V.
Secondary	1	H.M.	49	F	(±±±) Fever, Smell	Aspergillom	Asp. fumigatus	6				Not checked				Death	Amph. B 10mg I.V.
	4	U.K.	33	F	(±±±) Hemoptysis	Bronchus	Asp. fumigatus	355	↓		↓	X	128	X	128	Bay B 5907 Med.	Rt. Paraffin Plombage
	5	I.C.	55	M	(±±) Smell	Bronchus	Asp. fumigatus	133	↓	Smell(−)	↓	X	64	X	64	Biological Cure Bay B 5907 Med.	Amph. B (oral) 60 days Rt. Upper & Mid. Lobectomy, 1968
	6	S.H.	64	M	(±) Smell	Bronchus	Asp. fumigatus	150	↓	Hemoptysis(−)	(−)	X	16	X	16	Bay B 5907 Med.	Lt. Paraffin Plombage 1968
	7	S.Y.	63	M	(±) Smell	Bronchus	Candida albicans	77	(−)		(−)	(−)		(−)		Cured	Lung Abscess
	8	S.G.	32	F	(±)	Bronchus	Candida albicans	177	(−)		(−)	(−)		(−)		Cured	Lt. Pneumonectomy 1960
	9	M.S.	40	F	(±) Hemoptysis	Bronchus	Asp. fumigatus	180	unchanged		unstable	X	128	X	128	Bay B 5907 Med.	Bilat. Paraffin Plombage, 1967
	10	K.S.	29	F	(±)	Aspergillom	Asp. fumigatus	145	unchanged		unstable	X	8	X	8	Bay B 5907 Med.	
	11	I.T.	39	F	(±±)	Bronchus	Asp. fumigatus	159	(±)		(−)	X	8	X	8	Biological Cure Bay B 5907 Med.	Tailoring Thoraco-Plasty, 1957
	12	N.Y.	35	F	(±±)	Bronchus (cavity+)	Asp. fumigatus mucor	maintaining	unchanged		unstable Mucor(−)	X	8	X	8	Maintaining	
	13	K.A.	33	M	(±)	Bronchial Stump	Asp. fumigatus	25	unchanged		unstable	X	16	X	16	Bay B 5907 Med.	Rt. Upper Lobectomy 1969
	14	F.A.	21	M	(±)	Bronchus	Asp. fumigatus	27	unchanged		unstable	X	16	X	16	Bay B 5907 Med.	Lt. Lower Lobe Bronchiectasis
	15	T.J.	64	M	(++) Hemoptysis	Broncho-pulmonary	Asp. niger	51	unchanged		unstable	X	4	X	4	Bay B 5907 Med.	Primary (?)
	16	K.Y.	71	M	(±)	Bronchus (cavity+)	Asp. fumigatus	59	unchanged		unstable	X	8	X	8	Observation	
	17	F.Y	42	M	(++) Hemoptysis	Bronchus (cavity+)	Asp. fumigatus	65	unchanged		unstable	X	16	X	16	Bay B 5907 Med.	
	18	K.T.	48	M	(±)	Aspergillom	Asp. fumigatus					X	32			Observation	

(September 30, 1970)

Table 3. Clinical Results Treated with Bay-b 5097

Case No.	Age	Sex	Previous Treatment	Respiratory Symptoms	Lesion	Identification	Bay B 5097 mg/kg/d.	Total Dose	Max Serum Concent.	Effect Resp.	Effect Sympt.	Effect Colonies	Asp. fumig. C-F Test Pre	Asp. fumig. C-F Test Med.	Asp. fumig. C-F Test Post	Asp. fumig. C-F Test Med.	Toxic Reaction	Clinical Results
4	U.K.	33 F	Amph B Nystatin	(±±±) Hemoptysis	Bronchus	Asp. fumigatus	20→10→5	126 (g)	7.0 (γ/ml.)	↓	↓	↓ ↓	X	128	X	16	None	Improved Maintaining
5	I.C.	55 M	Amph B Nystatin	(±±)	Bronchus	Asp. fumigatus	20	111.6	8.0	↓ ↓	↓	–	X	64	(−)		None	Completely Cured
6	S.H.	64 M	Amph B Nystatin	(±)	Bronchus	Asp. fumigatus	20→15	87.5	5.5		↓	–	X	16	(−)		None	Completely Cured
9	M.S.	40 F	Amph B Nystatin	(+)	Bronchus	Asp. fumigatus Mucor	20→15→5	151	7.5		↓	↓ Mucor(−)	X	128	X	16	None	Improved Maintaining
10	K.S.	29 F	Amph B Nystatin	(±)	Aspergillom	Asp. fumigatus	20	88	6.5	Unchanged		Unstable	X	8	X	8	Skin Eruption	
11	I.T.	39 F	Amph B Nystatin	(±)	Bronchus	Asp. fumigatus	5	21.6	4.5		↓	–	X	8	(−)		None	Completely Cured
13	K.A.	33 M	Amph B Nystatin	(±)	Bronchial Stump	Asp. fumigatus	20	111.6	5.5		↓	–	X	16	(−)		None	Completely Cured
14	F.A.	21 M	Amph B Nystatin	(+)	Bronchus	Asp. fumigatus	20	100.8	6.0	↓	↓	–	X	16	(−)		None	Completely Cured
15	T.J.	64 M	Amph B Nystatin	(++) Hemoptysis	Broncho-pulmonary	Asp. niger	20	45.9	4.5	Unchanged		Unassessable	X	4	X	4	None	Discontinued by hope
17	F.Y.	42 M	Amph B Nystatin	(++)		Asp. fumigatus	20	6.2		Unchanged		Unassessable	X	16	X	16	Oligurea Proteinuria	Discontinued by hope
20	K.T.	44 F	Nystatin	Hemoptysis	Bronchus (cavity+)	Asp. fumigatus	20	3.2		Unchanged		Unassessable	X	8	X	8	Oligurea Homaturia	Discontinued
21	S.I.	26 F		(±)	Bronchus (cavity+)	Asp. fumigatus	20	122.4	7.5		↓	–	X	16	(−)		None	Completely Cured
22	O.S.	68 F		(++) Hemoptysis	Aspergillom	Asp. fumigatus	20→5	31.3	5.5		↓	Unstable	X	32	X	16	Eruption VIII. N. Palsy	Improved Maintaining
23	Y.N.	25 F		(±)	Bronchial Stump	Asp. fumigatus	20→10	67.5	7.0		↓	–	X	8	(−)		None	Completely Cured
25	T.S.	58 M		(±) Hemoptysis	Aspergillom	Asp. fumigatus	10→5	44.3	5.5		↓	Unstable	X	32	X	8	None	Maintaining
26	W.S.	54 M		(±) Hemoptysis	Bronchus	Asp. fumigatus	10→5	57.8	4.5		↓	(−)	X	16	(−)		None	Completely Cured
27	H.Y.	39 M		(+) Hemoptysis	Bronchus	Asp. fumigatus	10→5	65.4	5.0	Hemoptysis(−)		Unstable	X	16	X	8	None	Improved Maintaining
28	T.E.	29 F		(±)	Aspergillom	Asp. fumigatus	10→5	38.3	5.5	Hemoptysis(−)		Unstable	X	16	X	8	None	Improved Maintaining
29	M.K.	59 F		(±)	Bronchial Stump	Asp. fumigatus	5	19.4	4.5		↓	–	X	8	(−)		None	Completely Cured

(September 30, 1970)

Table 4.

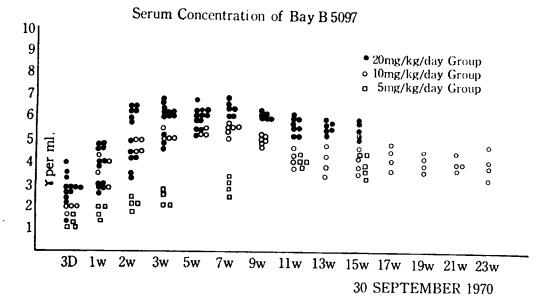
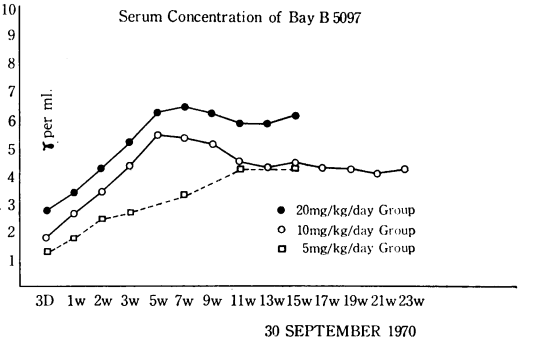


Table 5.



According to the information on Bay-b 5097 received, it is recommended that 20 mg/kg 3 times daily are administered. We treated 4 patients on the basis of this recommendation. We have observed decrease of urinary output occurred shortly after begin of treatment in all 4 cases, Hematuria and albuminuria in 2 cases, resulting in discontinuation of reuse of itself 2 cases medication stopped.

The other 2 cases responded well to diuretics, but complained of general fatigue and dysphoria. We, therefore, suspended further medication at this dosage in all 4 cases. The a. m. symptoms disappeared within 2 weeks after cessation of treatment. Due to this initial experience administration of Bay-b 5097 was resumed with a decreased dosage of 20 mg/kg daily divided into 3 single doses. We adjusted the dosage of Bay-b 5097 so, that effective serum levels of the substance were reached, which served as an index for therapy.

Laboratory tests (liver, kidney, blood) was carried out a regular intervals and shown in Tables 4, 5, 6, 7, 8 and 9.

The therapeutic results with Bay-b 5097 in 19 cases are shown in table 3.

Case histories, mycological findings, laboratory data and course of therapy with results were recorded in the provided patients' protocols. We consider 9 patients completely cured, 6 bettered and 2 cases as failures. Our definition "discontinued" means drop-out cases, which were transferred to other hospitals and cannot be followed up. We gained the impression that good or satisfactory results with Bay-b 5907 can be obtained if daily dosage is individually adjusted, so that serum levels are maintained at 4.5-5.0 gamma/ml. It has to be kept in mind that our patients are in the majority not in good physical condition and furthermore that in Japanese patients due to different constitution and dietary habits, when compared wiht Europeans, a lower dosage per kg body weight may have been suffice.

The concentrations of Bay-b 5097 in the patients' seraare shown in Table 4 (individually listed) and summarized in Table 5.

The following tables 6, 7, 8, 9, 10 and 11 show results of laboratory tests, which were done at regular intervals as recommended in the patients' protocols. Reproduced in the a. m. tables are ESR, leucocyte count, alk. phosphatase, serum potassium, serum cholesterol and in Table 11 a summary of all findings done in form of graph are presented.

Detailed information on all laboratory findings as listed in the patient's questionary can be derived from those.

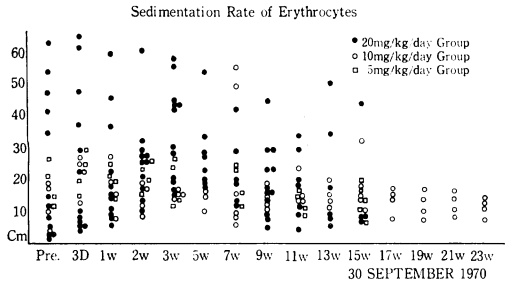
From the above table, which shows mean values of laboratory tests in which any changes were observed, it can be derived that changes reach peaks in the 1. and/or 2. week after start of medication and thereafter tend to be gradually restored to pre-medication levels.

Changes necessitating cessation of treatment with Bay-b 5097 were not observed.

We wish to present in more detail 2 cases, who in our opinion demonstrate rather clearly the efficacy of Bay-b 5097 on one hand, on the other also substantiate our opinion of reduced dosage for Japanese patients.

Case No. 22 (of table 3)

Table 6.



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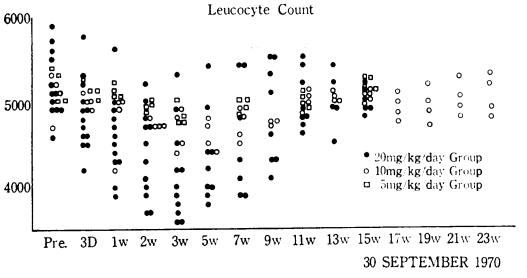

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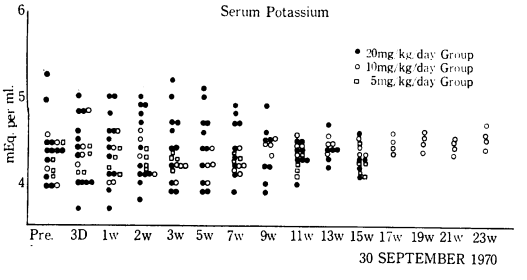

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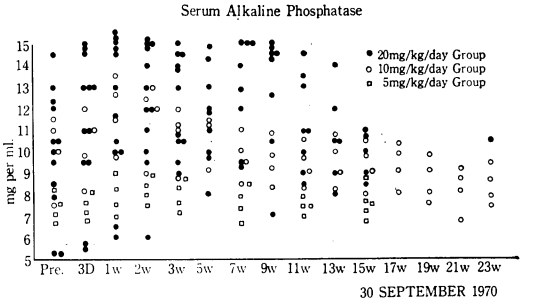


Table 10.

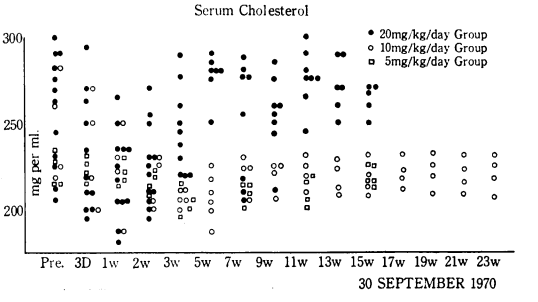
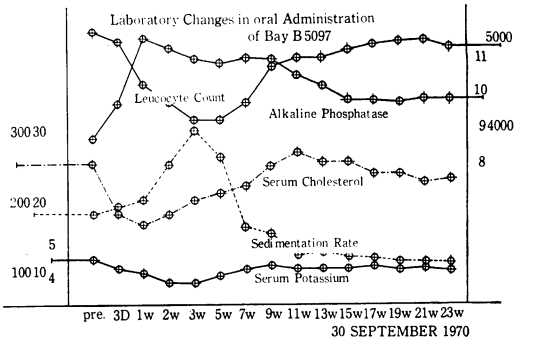


Table 11.



Case No. 22 (of Table 3) -1

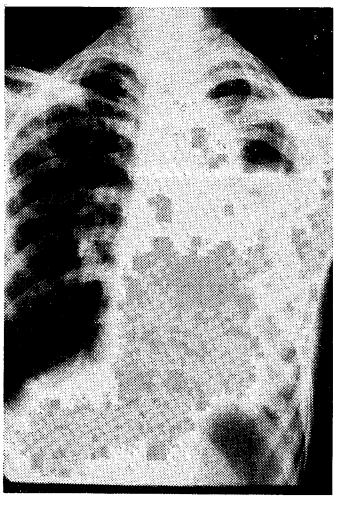
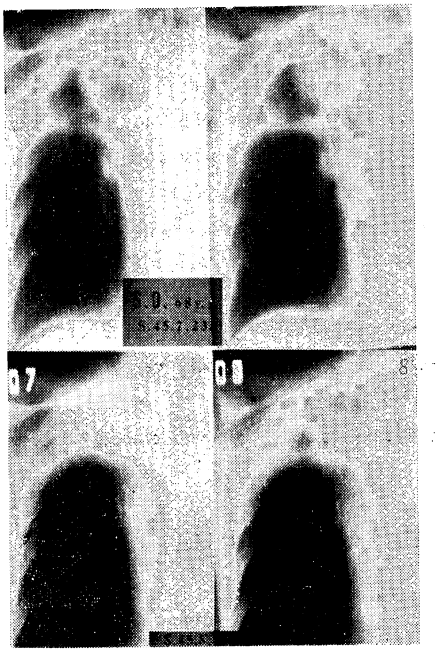


Table 12.

Patients' Data	Bay-b 5097 Treatment			Side-effects observed								Tolerance Remarks
	20 mg/kg days	10 mg/kg days	5 mg/kg days	Gastro-Intest.	Allergic	Fever	Oliguria	Hematuria	Protein uria	Ureth. Burn	Others	
U.K. 33 F	90	90	90									Poor initially now good
I.C. 55 M	90											Perfect
S.H. 64 M	60	30								x		Perfect
M.S. 40 F	90	90	90									Perfect
K.S. 29 F	10				x	x						Poor with-drawal
I.T. 39 F			114									Perfect
K.A. 33 M	90											Perfect
F.A. 21 M	90									x		Perfect
T.J. 64 M	45	(Transferred to other hosp. Not to be judged)								x		Perfect
F.Y. 42 M	5	(Psychologically instabile drop-out case)					x		x			Not to judge
K.T. 44 F	4	(Exitus due to other causes after 4 days)					x	x				Not to judge
S.I. 26 F	120											Perfect
O.S. 68 F	14		90		x	x					Facial palsy	Poor initially now good
Y.N. 25 F	60	30										Perfect
T.S. 58 M		60	30									Mederate
W.S. 54 M	90	30								x		Perfect
H.Y. 39 M		90	30							x		Perfect
T.E. 29 F		90	30									Perfect
M.K. 59 F	90											Perfect

Case No. 22 (of Table 3) -2



A 68 year old female height 1.50 m and 43.0 kg bodyweight an inpatient of our hospital developed pulmonary Aspergillosis after lung-abscess.

Aspergillus fumigatus was cultured from bronchial secretino and sputum, completement fixation tests confirmed the tentative diagnosis. Roentgenographically a characteristic "fungus-ball" was detected (see x-ray below.

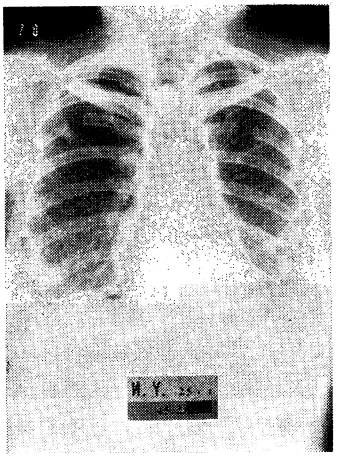
The patient received Bay-b 5097 in a daily dose of 20.0 mg/kg for 14 days and serum levels of 5.5 gamma/ml were reached.

During medication a skin-rash broke out over the whole body surface and lesions in the oral mucosa were seen. Rise of temperature.

Unilateral facial paralysis developed and Bay-b 5097 treatment with the a. m. daily dosage was suspended. All symptoms disappeared under appropriate medication whthin one month and Bay-b 5097 treatment was continued with a dosage of 5.0 mg/kg/d.

Serum levels of approx. 4.5 gamma/ml were maintained with this regimen and no side-effects whatsoever

Case No. 23 (of Table 3)



observed during the subsequent course of Bay-b 5097 medication lasting for 4 more month.

The roentgenogram below shows patient's status in Sept. 1970.

Case No. 23 (of table 3)

A 25 year old female (height 1.45 m, weight 45.0 kg) with pulmonary tuberculosis had undergone right/upper lobectomy in March 1967 and left/upper lobectomy in October of the same year.

The roentgenogram below shows patient's status postoperatively. A fungal infection at the left bronchial stump was suspected and the diagnosis confirmed by direct specimen and culture of sputum and bronchial secretion, complement fixation tests leading to the identification of the pathogen as Asp. fumigatus.

Bay-b 5097 treatment was stared with 20.0 mg/kg/d for 60 days and with 10.0 mg/kg/d for 30 more days.

Serum levels of Bay-b 5097 reached values of 4.4 gamma/ml up to the eleventh week.

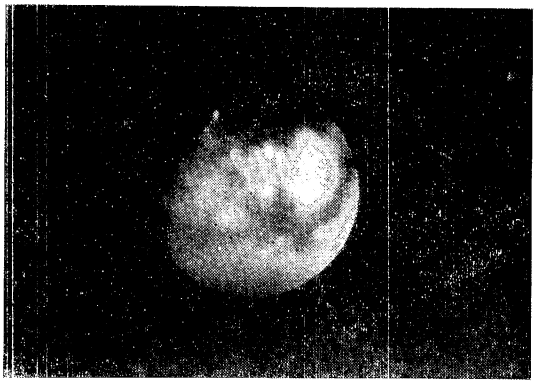
The patient tolerated the medication with Bay b 5097 very well and no allergic or toxic reactions were observed.

The healing process of the bronchial stump lesion was traced by bronchofiberscopy and color slides taken at various stages.

Picture 1 (before treatment)

A grayish-blue fungal mass adherent to the bronchial stump.

Picture 1. (before treatment)

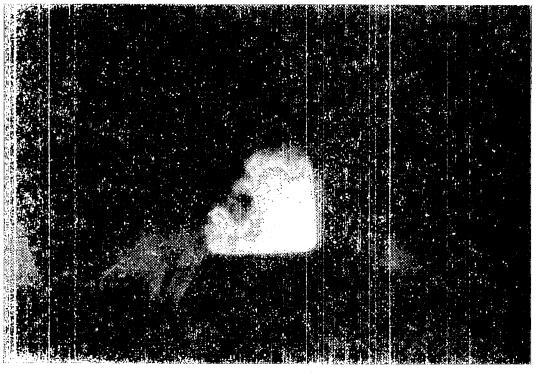


A grayish-blue fungal mass adherent to the bronchial stump.

Picture 2 (after 1 month treatment Bay-b 5097)

The fungal mass has disappeared and dirty-brown granules can be observed.

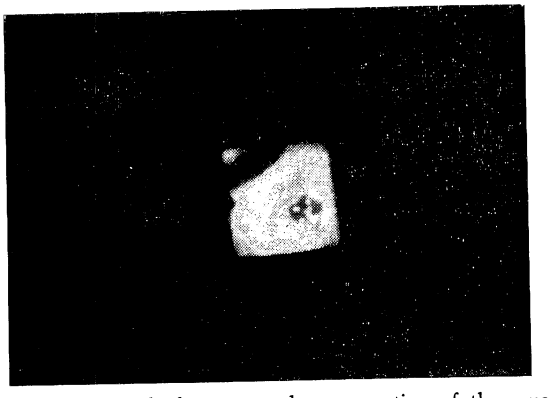
Picture 2. (after 1 month treatment Bay-b 5097)



The fungal mass has disappeared and dirty-brown granules can be observed.

Picture 3 (after 2 months treatment with Bay-b 5097)
Beginning of exfoliation at the bronchial stum and regeneration of the mucous membranes.

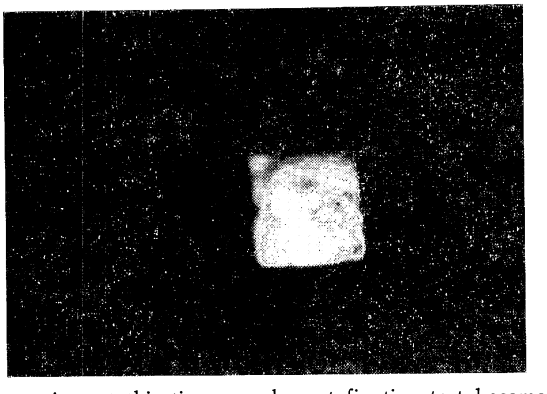
Picture 3. (after 2 months treatment with Bay-b 5097)



Beginning of exfoliation at the bronchial stump and regeneration of the mucous membranes.

Picture 4 (after 3 months treatment with Bay-b 5097)
Further regeneration, at this time complement fixation test became negative.

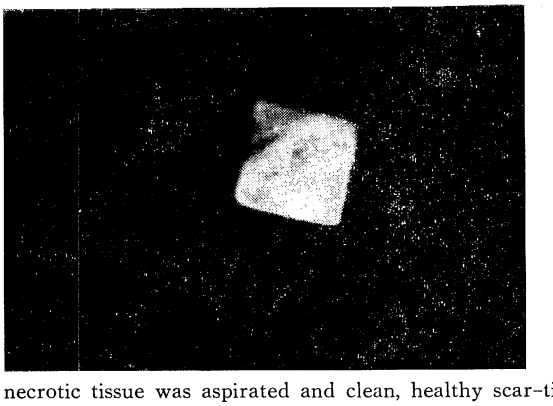
Picture 4. (after 3 months treatment with Bay-b 5097)



Further regeneration, at this time complement fixation test became negative.

Picture 5
The exfoliative, necrotic tissue was aspirated and clean, healthy scar-tissue is seen.

Picture 5.



The exfoliative, necrotic tissue was aspirated and clean, healthy scar-tissue is seen.

During the course of treatment with a new substance as Bay-b 5097 is, our attention was focused especially on the clinical tolerance and side effects. The patients treated were in the majority chronically ill and in retired physical condition. Therefore, the laboratory tests required were carried out prior and during treatment as outlined in the patients' protocols. On the whole, Bay-b 5097 showed a good tolerance. Gastrointestinal disturbances such as nausea, anorexia and vomiting were observed only initially when a higher dosage of the substance (i.e. 60 mg/kg/day) was given. Out of 19 patients treated with Bay-b 5097 15 tolerated the substance very well. Only in 4 cases were side effects observed. Table No. 12 gives detained information of Bay-b 5097 dosage administered, duration of treatment, side effects observed and judgement on tolerance. From it can be derived that skin eruptions and fever were observed in 2 patients, oliguria 2 times, hematuria 1 time and proteinuria 1 times in 2 patients which dropped out of treatment due to other causes then substance related. In 6 male patients initially a burning sensation when passing urine was noted which subsided after 1-2 weeks continued treatment. We have described the skin rush and lesions in the oral mucosa followed by facial paralysis in 1 case (No. 22 of table 3).

Summary

A report is given on the therapeutic results obtained with a new antimycotic substance Bay-b 5097, Tritylimidazole derivative, in 19 cases of pulmonary Aspergillosis. The substance during our clinical trial was found to be very effective. Tolerance assessed by tests of the hepatic and renal functions and examination of blood status was found good even during prolonged administration. We were able to achieve complete cure in 9 and clinical improvement in 6 cases. The dosage has to be adjusted invidually according to so that optinral it has been our impression individual dosage adjustment serum levels of active Bay-b 5097 is reached.

The results we obtained suggest that Bay-b 5097 has a considerable potential effectiveness in the treatment of human mycotic diseases side effects attributed to the substance are not severe. We believe Bay b 5097 has in-ted a decisive progress in therapy.