Acta virol. **24**: 279–290, 1980

EARLY AND DELAYED SKIN REACTIVITY TO SOLUBILIZED ANTIGENS OF HERPESVIRUS HOMINIS 1 IN PSYCHIATRIC PATIENTS AND GUINEA PIGS

H. LIBÍKOVÁ, *J. POGÁDY, **L. KUTINOVÁ, *Š. BREIER, J. MATIS

Institute of Virology, Slovak Academy of Sciences, 809 39 Bratislava; * Psychiatric Research Laboratory, Research Institute of Medical Bionics, Pezinok; and **Institute of Sera and Vaccines, Prague, Czechoslovakia

Received March 13, 1980

Summary. — Intradermal tests with a mixture of Herpesvirus hominis 1 (HVH 1) antigens containing quantitated neutralization antigen were done in 39 schizophrenics (SCH), 42 senile demented (DS) persons, 28 alcoholics, neurotics and psychopaths (ANP) and 33 control persons. Local induration, erythema and fading was evaluated according to diameter and intensity after 15 to 30 min for anaphylactic type I reaction, after 5 hr for Arthus type III reaction and after 24 and 48 hr for delayed hypersensitivity (type IV). The diagnosed clinical forms influenced the incidence of positive reactions I, III or IV at the level $\alpha = 0.01$. The incidence of positivity in all reactions (I, III plus IV) was significantly higher in the patients than in the control group. Type I and III reactions were most intensive in ANP and SCH, respectively. Type IV reaction was most pronounced in SCH, including the highest incidence of purple lesions, eventually with a lightly cyanotic target. In the DS group, type IV reaction surpassed the control the least of all patients' groups. Unfavourable side effects of the skin tests were not observed. The importance of repeated contact with HVH 1 for a marked type IV reaction was confirmed in experimentally infected guinea pigs, which also served for safety tests and selection of antigen preparations.

Key words: psychiatric patients; guinea pigs; skin tests; Herpesvirus; anaphylaxis; delayed hypersensitivity; Arthus reaction

Introduction

The aim of this study was to obtain information on hypersensitivity of various groups of humans to HVH 1 neutralization antigens against which practically all adults in Slovakia have serum antibodies (Libíková *et al.*, 1976). HVH 1 is a lifelong companion of us. Humoral immunity to HVH 1 is frequently elevated in neuropsychiatric patients who have complement-

dependent HVH 1 neutralizing antibodies often also in the cerebrospinal fluid (Libíková *et al.*, 1979*a*). Such facts evoke the question as to how does this humoral immunity correlate with eventual immediate and delayed cell-mediated hypersensitivity or with the readiness to form specific immune complexes. Skin tests evaluated after various time intervals (Pepys, 1975) may provide broad information in this sense. Our work was based on the use of a non-infectious preparation of HVH 1 antigens containing exactly quantitated amounts of neutralization antigen (Kutinová *et al.*, 1977, 1979). It was shown acceptable for clinical use also by preliminary assays in guinea pigs.

We examined 33 control persons and 112 patients with functional and organic psychoses and with less severe mental disorders. The results contribute to the viral hypotheses of psychiatric disturbances (Rimón *et al.*, 1971; Fuller-Torrey and Peterson, 1976; Libíková *et al.*, 1976, 1979*b*; Fuller-Torrey *et al.*, 1978).

Materials and Methods

Viral antigens. *a*) Formalin-inactivated HVH 1 (HVH vaccine) in medium from infected cell cultures, dialysed, was supplied by Dr. R. Benda, Military Institute of Hygiene, Epidemiology and Microbiology, Prague. This preparation had been administered to approx. 100 persons with the aim to prevent attacks of recurrent herpes labialis. Control antigen from equally treated uninfected cultures was also available *b*) HVH 1 neutralization antigen (N-Ag), in a mixture of solubilized HVH 1 antigens, was prepared from infected human diploid cells treated with Nonidet-P 40, ultracentrifuged and extensively dialysed (Kutinová *et al.*, 1977). In addition, the preparation was treated with 0.015 % formalin at 37 °C for 24 hr and formalin was removed by dialysis at 4 °C for 48 hr against phosphate buffered saline (PBS). The content of N-Ag was determined by the ^{51}Cr release inhibition test (CRIT, a cytotoxicity inhibition test, Kutinová and Vonka, 1978). One CRIT unit is the least amount of antigen causing 50 % inhibition of ^{51}Cr release from HVH 1-infected rabbit target cells. Control antigen was prepared from similarly treated uninfected cells. *c*) HVH 1 envelope antigen (E-Ag) from purified virions prepared by Nonidet-P 40 treatment (final concentration 0.5 %; Leššo *et al.*, 1976). The effect of Nonidet-P 40 was controlled by intradermal injection of 0.05 ml of a 0.5 % aqueous solution (control to E-Ag).

Skin tests in guinea pigs (300—400 g or more). HVH 1 clone 70 (Rajčáni *et al.*, 1969) in a dose of 10^4 mouse LD_{50} was administered by intraplantar inoculation at various intervals before the skin test. An area approximately 5 × 9 cm of the ventral skin was smoothly depilated with "Depilas" cream (SPOFA). The viral and control antigens were injected 24 hr later intradermally on the left and right side of the depilated area, respectively. The inoculum contained 3—4 CRIT units of N-Ag in 0.02 ml.

Skin tests in humans. The examined patients did not suffer from any febrile illness and, in general, were somatically healthy with the exception of the senile demented ones, some of whom had usual troubles of the elderly. Disposable syringes and needles No. 22 were used for intradermal injection of 9—10 CRIT units of N-Ag in 0.05 ml and of an equal volume of similarly diluted control antigen in the right and left fore-arm, respectively. Some persons were simultaneously tested with E-Ag in the same way. Blood samples were obtained by venepunction just before and 2 to 7 days after the skin test.

Evaluation of the skin reaction. Reading was performed for the anaphylactic reaction after 15—30 min, for the Arthus reaction after 5 hr and for delayed-type hypersensitivity after 24 and 48 (sometimes also 72) hr. The diameter of induration (IN) and erythema (ER) was measured in mm. Intensity of the reaction was scored 0 — negative, 1 — pink and soft, 2 — red and obdurate, 3 — purple and very hard for ER and IN, respectively, If the skin around ER was faded, the pale area was measured in mm. The sizes of ER and IN were evaluated separately or statistical averages were calculated for the groups studied. "Global" reaction, i. e. a sum of all data described above was scored from 0 to 13. For this purpose, the dimensions were scored as follows. For IN

< 5 mm — 0; 5 to 9 mm — 1; 10 to 20 mm — 2; and > 20 mm — 3. For ER: < 10 mm — 0; 10 to 19 mm — 1; 20 to 30 mm — 2; 31 to 50 mm — 3; and > 50 mm — 4.

Neutralization test with HVH 1 was carried out in chick embryo cell cultures with 100 CPD_{50} of a cytopathic HVH 1 strain without and with complement for the detection of complement-independent (C—) and complement-dependent (C+) antibodies, respectively (Libíková *et al.*, 1979*a*, *b*).

Detection of circulating immune complexes (PEG-IKEM test) was done by selective precipitation with polyethylene glycol 6000 (Serva) and photometric evaluation according to Hašková *et al.* (1977). Unfrozen sera stored at 4 °C for not more than 1—3 days were examined.

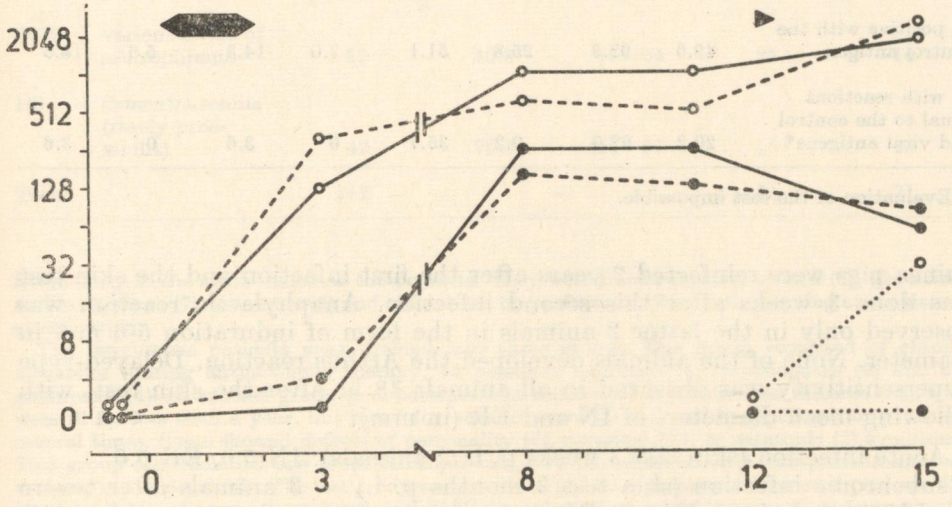

Fig. 1.

Neutralizing antibodies in guinea pigs after intraplantar infection with HVH 1 and after skin test with N-Ag

Infection at time 0, skin test at week 12.

Abscissa: time in weeks; ordinate: antibody titres (○ C+, ● C— antibodies)

——— Response of guinea pig No. 4

— — — Mean response of 14 guinea pigs

. . . . Mean antibody response to the skin test of 3 guinea pigs previously not infected with HVH 1.

Black areas above the curves: local lesion development after intraplantar infection (left) and skin test (right)

Results

Experiments in guinea pigs

Local reaction to HVH 1 intraplantar infection was not uniform in all infected animals. Some developed typical herpetic lesions with central necrosis, others reacted only with oedema and erythema. Antibody response (Fig. 1) confirmed the known priority of C+ antibodies at early intervals. Severity of the local lesions did not influence the antibody titres. Skin tests with N-Ag were carried out 3 weeks and 3 months after HVH 1 infection. Two

Table 1. Nonspecific skin reactions to control antigens

Findings	Type of reaction I 20—30 min		III 5 hr		IV 24 hr		48 hr	
	N-Ag	E-Ag	N-Ag	E-Ag	N-Ag	E-Ag	N-Ag	E-Ag
No. of persons examined	119	28	118	28	115	28	107	27
% positive with the control antigen	49.6	92.9	25.8	51.1	7.0	14.3	5.6	18.5
% with reactions equal to the control and viral antigens*	20.2	92.9	9.2	35.7	0	3.6	0	3.6

* Evaluation of the test impossible.

guinea pigs were reinfected 2 years after the first infection and the skin test was done 3 weeks after this second infection. Anaphylactic reaction was observed only in the latter 2 animals in the form of induration 5-6 mm in diameter. None of the animals developed the Arthus reaction. Delayed-type hypersensitivity was observed in all animals 48 hr after the skin test, with following mean diameters of IN and ER (in mm):

Acute infection (skin test 3 weeks p. i., 2 animals): IN 5.0, ER 5.0;

subchronic infection (skin test 3 months p. i.) — 3 animals after severe local herpetic lesions: IN 1.7, ER 3; 3 animals after moderate local herpetic lesions: IN 4.0, ER 4.7;

chronic infection and acute superinfection (skin test 2 years after infection and 3 weeks after superinfection, 2 animals): IN 4.0, ER 7.5.

Comparison of three HVH 1 antigen preparations in skin tests

In a few guinea pigs, HVH vaccine, N-Ag, E-Ag and their controls were skin-tested, all simultaneously in each animal. The three antigens yielded similar results; E-Ag induced more nonspecific reactions than HVH vaccine nad N-Ag.

The HVH vaccine was not used in humans to avoid the administration of whole virions. N-Ag and its control was tested in 119 persons and 28 of them simultaneously were given also E-Ag and its control. Both types of control antigen induced some nonspecific reactions — mainly immediate (Table 1). N-Ag appeared more convenient and was chosen for examinations in humans. All subsequent data are based on the use of N-Ag.

Characterization of the groups studied

All examined patients were hospitalized in the Regional Psychiatric Hospital in Pezinok. The control group was composed of 33 members of the staff of this hospital, who were staying for many

Table 2. Characteristics of the groups studied

Group	Total	Age in years		Sex	
		Average	Range	Males	Females
C — control	33	37.4	20—61	11	22
ANP — alcoholism, neurosis, psychopathia	28	38.2	22—72	19	9
SCH — various forms of schizophrenia	39	40.0	19—64	25	14
DS — dementia senilis (rarely praesenilis)	42	70.8	44—87	16	26
Total	142		—	71	71

hours daily in the same milieu as the patients. They were nurses (8), technicians (7), physicians and researchers (7), labourers (6) and officials (5) by profession, all actively working at the date of examination.

The psychiatric patients were divided into three groups. One group consisted of chronic alcoholics (during antialcoholic therapy, 14 persons), neurotics (4), psychopaths (6) and oligophrenics (4). In another group were patients with schizophrenia and related diseases (39). Five were ill for less than a year, but most for several years (2—35) and hospitalized for psychosis several times. Some showed defects of personality (6), paranoid (19) or catatonic (2) symptoms. This group also included one propf-schizophrenia, two paraphrenias, one hebephrenia and one schizoaffective psychosis. The last group were senile or (seldom) praesenile demented persons (42). Many had signs of cerebral arteriosclerosis (13), some showed paranoid (9 persons) or depressive (6) syndromes, two were alcoholics. Pick and Jakob-Creutzfeldt diseases were not, but 2 cases of Alzheimer disease were included.

Sex and age of persons in the four groups is given in Table 2.

Anaphylactic reaction

Immediate type I skin reaction is caused by release of histamine and other active substances and correlates with the state of vegetative nervous system. The skin of some individuals shows hypersensitive reactions to nonspecific stimuli, e. g. to our control antigens. Early reactivity could not be evaluated in 20 % of persons because of nonspecificity. Specific reactions were found in 80 % of persons (Fig. 2-I and II). ER was less frequent in controls than in the other groups ($\alpha = 0.025$) and was also less intensive. ER of $\leqq 40$ mm in diameter did not appear in the control group. The incidence of IN in the control group was low as compared with that in the patients ($\alpha = 0.05$), and was significantly higher in the ANP than in the DS group ($\alpha = 0.05$). In the ANP group, the frequency and intensity of IN was higher than that of ER, as distinct from all other groups. Two demented, one alcoholic and one psychopathic patient revealed dominant anaphylactic reaction and negative or futile delayed hypersensitivity. Opposite findings were more frequent: 7 controls, 3 ANP, 3 SCH and 3 DS patients had unchanged skin after 30 min

and pronounced delayed reaction (global 6 and more). So far, we could not differentiate between atopic and sensu stricto anaphylactic reaction.

Arthus reaction in relation to circulating immune complexes

Positive type III reaction may indicate the readiness to formation of immune complexes with the respective antigen. Fig. 2-III and IV shows a markedly higher frequency of Arthus reaction in the patients' than in the

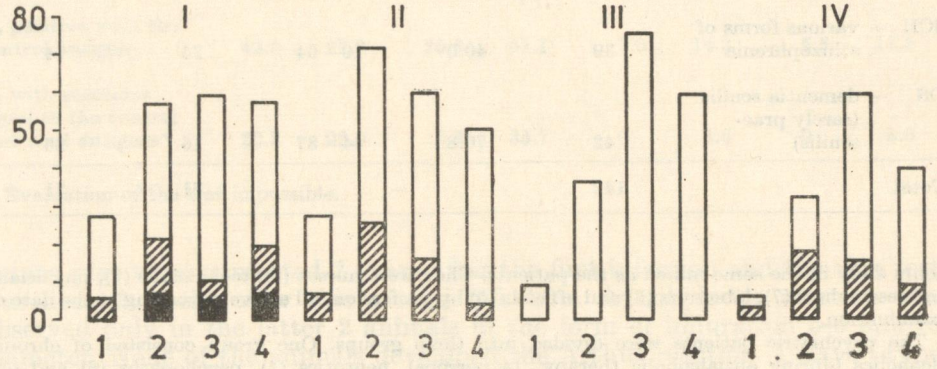

Fig. 2.

Early skin hypersensitivity to HVH 1 N-Ag in humans
I and II — anaphylactic type I reaction (I-ER, II-IN) III and IV — Arthus type III reaction (III — ER, IV — IN) Columns 1, 2, 3 and 4; groups C, ANP, SCH and DS, respectively
Ordinate: % of positive reactors (empty areas) or % of ER and IN with diameters of 20—39 mm and > 10 mm, respectively (shaded areas) or % of ER with a diameter > 40 mm (black areas).

control group. IN was significantly less frequent in controls than in patients ($\alpha = 0.01$). ER was less frequent ($\alpha = 0.025$) and markedly less frequent ($\alpha = 0.01$) in controls than in the ANP group and the SCH plus DS group, respectively. The indurations in this reaction used to be soft, oedematous and they reached extreme diameters of 35—40 mm in two demented patients. We searched also for the fading of skin around the ER which is a consequence of cellular infiltration. Such fading has never been observed in control persons, but was recorded in 32 % SCH, 14 % DS and 12 % ANP patients. Persons with pronounced Arthus reaction showed before the skin test high values of circulating immune complexes in the PEG-IKEM test — 2-5 times surpassing the norm in controls which in our conditions was approx. 20.

Delayed-type hypersensitivity

Type IV reaction which measures cell-mediated immunity provided by sensitized lymphocytes was observed in most persons in all groups, at least as concerns ER (Fig. 3). But the incidence of reactions — both ER and IN — in control persons was lower than in any test group ($\alpha = 0.05$). Moderate and

strong reactions used to culminate 24 and 48 hr after the skin test, respectively, but after 72 hr all reactions were already disappering or absent. Culmination after 48 hr was observed in 26—33 % of persons in the control, ANP and SCH groups and in 12 % of DS patients. Maximal ER were observed in the SCH group, maximal IN — hard and well bordered — in the ANP group.

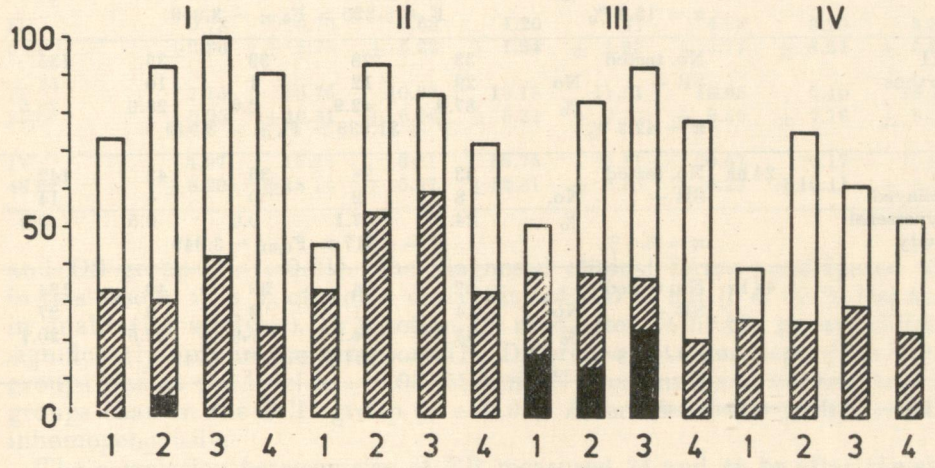

Fig. 3.
Delayed hypersensitivity (type IV reaction) to HVH 1 N-Ag in humans
I and II — ER (I) and IN (II) after 24 hr III and IV — ER (II) and IN (IV) after 48 hr. Other designations as in Fig. 2.

ER with a smaller cyanotic target in the centre was observed in 28 % SCH, 15 % ANP and in 2—3 % DS and controls. The diagnosed clinical forms influenced significantly the incidence of such lesion ($\alpha = 0.01$). Probability of such lesion was lower in the DS and control group than in the SCH group ($\alpha = 0.005$). Intensively red but not cyanotic ER scored 3 was observed in 3 % control, 15 % ANP, 28 % SCH and 24 % DS persons. The probability of degree 3 ER was lower in controls than in DS and SCH patients ($\alpha = 0.01$).

The largest reaction in the course of this study was observed in a 32 years old schizophrenic woman with paranoid syndrome (L. M.): ER 75 mm with a 32 mm cyanotic target and 20 mm IN developed within 48 hr. The patient had also a strong anaphylactic reaction with ER 55 mm and IN 13 mm in diameter. Arthus reaction was negative.

Statistical evaluation of type I, III and IV reactions

Qualitative analysis (Table 3) of dispersion (sigma) of the incidence of IN or ER or fading, single or in combination at a given time interval [$\text{sigma}^2 =$

Table 3. Statistical analysis of the incidence of absent skin reactivity to HVH 1 N-Ag in the groups studied

Type of reaction				Group Control	ANP	SCH	DS	Total
I		No. tested		33	28	39	42	142
Anaphylactic		SR —*	No.	21	6	7	10	44
			%	63.6	21.4	17.9	23.8	31.0
		$\pi = 15.3$ %		$F = 8.325 > F_{0,01} = 3.949$				
III		No. tested		33	28	39	35	135
Arthus		SR —	No.	29	12	1	10	52
			%	87.9	42.9	2.6	28.6	38.5
		$\pi = 42.2$ %		$F = 31.838 > F_{0,01} = 3.949$				
IV	24 hr	No. tested		33	28	39	42	142
Delayed		SR —	No.	8	2	0	4	14
hypersensi-			%	24.2	7.1	0.0	9.5	9.9
tivity		$\pi = 8.4$ %		$F = 4.317 > F_{0,01} = 3.949$				
	48 hr	No. tested		32	24	38	40	134
		SR —	No.	14	1	3	9	27
			%	43.8	4.2	7.9	22.5	20.1
		$\pi = 13.8$ %		$F = 6.964 > F_{0,01} = 3.949$				

* SR — = skin reaction absent.

$= n \times p\ (1\text{-}p)$; p = probability of the absence of any reaction] allowed the following conclusions. The diagnosed clinical forms influenced the incidence of positive reaction of any type at the level $\alpha = 0.01$. Participation of the diagnosed forms in global variability of percentage of positive results was the highest in reaction III ($\pi = 42.2$ %). Absence of reaction was the most probable in the control group for all three types of reaction. If the dispersion was analysed for the three patient groups only — excluding the control group —, then the significance of diagnosed clinical form for the incidence of positive skin reaction was maintained solely in reaction III ($\alpha = 0.01$). Participation of the diagnosed clinical form in global variability of percentage of positive results was low: $\pi = 15.9$ %. In reactions I and IV, the differences between the patient groups did not surpass the limits of occasional fluctuation.

Data on IN and ER were analysed quantitatively based on mean diameters (MD) in mm and standard deviations (SD) of both symptoms (Table 4). Patients with fading of the skin were excluded. In reaction I, all four groups and only the three patient groups were homogeneous for IN and ER, respectively. MD of IN was higher in the ANP than in the DS and control groups ($\alpha = 0.025$). MD of ER was smaller in controls than in pooled patient groups (MD = 9.05 mm, SD = 12.97, $\alpha = 0.025$). In reaction III, the groups reacted inhomogeneously as concerns both IN and ER. ER could be evaluated in control, SCH and DS groups. MD of ER was lower in control than in SCH

Table 4. Mean diameters ± standard deviations (mm) of induration (IN) and erythema (ER) in skin reactions I, III and IV in the groups studied

Type of reaction	Group							
	Control		ANP		SCH		DS	
	IN	ER	IN	ER	IN	ER	IN	ER
I	1.91	4.03	5.68	11.14	3.61	8.00	3.26	8.62
20–30 min	±3.27	± 7.88	± 4.23	±13.41	± 4.53	±12.37	± 3.99	±12.82
III	0.73	0.70	2.68	1.20	1.31	4.96	3.20	3.38
5 hr	±2.96	± 2.75	± 5.22	± 1.94	± 1.95	± 3.77	± 8.64	± 3.63
IV	7.15	16.76	10.93	18.15	11.21	18.65	7.10	15.19
24 hr	±9.95	±10.31	± 6.69	± 9.31	± 7.73	± 9.56	± 7.18	± 9.53
IV	4.97	15.28	6.21	16.75	6.11	20.67	6.17	10.97
48 hr	±8.20	±18.16	± 5.47	±12.81	± 6.15	± 6.23	±10.11	± 8.77

and DS groups ($\alpha = 0.01$). The diagnosed clinical forms participated also in this case in 21.8 % of global variability of MD of ER (i. e. 50 % less than in qualitative analysis). In reaction IV read after 24 hr the groups differed significantly only in the symptom IN. Difference between dispersions in the groups was at the level $\alpha = 0.05$. MD of IN was smaller in control and DS groups than in the SCH group ($\alpha = 0.01$). After 48 hr, the groups reacted inhomogeneously.

The correlation between size of ER measured 24 and 48 hr after the skin test was high in all groups ($\alpha = 0.01$). On the contrary, the size of IN after 24 and 48 hr did not correlate. (Calculated by simple linear correlation.)

We observed no significant influence of sex on the skin reactions. As concerns the relation to age in the control group, the mean global of reaction I was the lowest in 20–29 years old persons and increased gradually with age till 69 years, while that of reaction IV in the youngest and oldest (50–69) persons was lower than in the middle aged (30–49) ones.

All reactions were completely negative in six persons without serum HVH 1 antibodies, but also in two demented and one control person (22 years) who were serologically positive. A marked difference between the patient groups and the control group was observed for positivity of reaction I, III plus IV in one person, namely: control – 3 %, ANP – 48 %, SCH – 53 %, DS – 49 % ($\alpha = 0.005$, $F\ 9.14 > F_{0.01}$).

Comments on the control group

All control persons were "healthy" at work at the date of skin tests, but many had occasionally suffered from recurrent troubles as herpes labialis (52 %), cervico-cranial syndrome (33 %), migraine (36 %), or psychic depression (18 %). An accumulation of herpes labialis, cervico-cranial syndrome and migraine was registered in 15 % of persons. Only 30 % of controls claimed themselves continually healthy. Skin tests in this subgroup were

negative but in one 57 years old person with marked delayed hypersensitivity (global 9), who claimed himself aggressive and even furious in anger. Otherwise, globals of all types of skin reactions were higher in the recurrently ill than in the "absolutely healthy" controls. However, the whole control group represented an accidentally chosen sample of our working population and was used as a comparative set.

Subjective and objective side effects of the skin tests with N-Ag

Almost all persons tested revealed no unfavourable effects. No febrile reactions were observed. Local sensations were not reported but in three patients: two with local itching and one with a slight and temporary local pain in a moderately intensive reaction IV.

HVH 1 neutralizing antibodies assayed with and without complement and circulating immune complexes were examined in paired sera taken before and 2 to 7 days after the skin test from 20 patients. Antibody titres did not substantially change. The slight variations — twofold drop or increase in titre — did not surpass the longitudinal variation in untreated persons. Only two schizophrenics showed a marked drop of C+ antibody titre two days after the skin test. In these cases, antibodies were perhaps bound to the injected antigen and immune complexes were cleared from circulation or phagocytized — values of circulating immune complexes were somewhat lower after than before the skin test, like in the other persons tested.

Discussion

Skin tests with viral antigens have been used for diagnostic, immunological and prophylactic purposes, e. g. in mumps (Enders *et al.*, 1946) or pseudorabies of pigs (Škoda *et al.*, 1968). Nagler (1946; cit. after van Rooyen and Rhodes, 1948, p. 189) and others used heated HVH 1 from chick embryonic fluids for skin tests in humans and found a correlation with seropositivity.

We do not assume that an altered immune response would depend directly on psychopathological symptomatology of the given clinical form. However, participation of the limbic system and of hypothalamic structures in the aetiopathogenesis of psychopathological symptoms was proved and these structures use to reveal functional disorders and organic lesions in mental illness. Also primary and secondary immune response and its modulations are conditioned by the functional stage of hypothalamic and limbic structures (Korneva, 1976). Thus, alteration of immunity reactions may reflect indirectly the psychiatric symptomatology, mainly affective, emotional and instinctive manifestations.

Anaphylaxis is antibody-dependent and due to liberation of small molecular weight mediators. Most pronounced anaphylactic hypersensitivity to N-Ag was found in the ANP group. We intend to assay also other viral antigens and eventually use antihistaminic drugs.

Hypersensitivity from immune complexes is detectable by skin tests when precipitating antibody is availabe in excess with respect to the amount

of antigen. High incidence of this reaction in schizophrenics and senile demented is in agrement with elevated humoral immunity to HVH 1 (Libíková *et al.*, 1976).

Delayed hypersensitivity to N-Ag was high in all groups of mentally ill persons, but least in senile demented ones. This corresponds to the general decline in skin reactivity after the age of 50 years (Walford, 1967). But the kinetics of lesion development was not retarded in the elderly demented patients, maximal reactions were already observed after 24 hr.

Data are accumulating on HVH 1 or HVH 1 antibody detection in the CNS of chronic neurological and psychiatric patients and of controls (Fuller-Torrey *et al.*, 1978; Gajdusek, pers. comm. 1979; Rimón *et al.*, 1979; Libíková *et al.*, 1979*a*, *b*; Sequiera *et al.*, 1979). We may ask whether the brain is capable of at least partial analogous hypersensitivity reactions as the skin. Both organs originate from ectoderm. Autoallergic attacks on the CNS have been discussed in connection with chronic viral infections (Oldstone and Dixon, 1976), viral antigens in cells being the "not-self" component. Futile allergic disturbances are also to be presumed. Ado (1978, pp. 310—345) considers the neural system as a tissue which can be sensitized and which may participate in all degrees of allergic reactions. Noxious immunological mechanisms are ready in mentally ill and to a lower degree also in healthy persons, but crucial seems to be the CNS itself: whether and where does exist the tissue target marked by the HVH 1 antigens. If it exists and is localized in a functionally important area (Libíková *et al.*, 1979*b*), the disorders may develop. Whether the inadequate immune response to HVH 1 was induced by stress of mental illness or vice versa, remains unresolved. Some data indicate that at least the relapses e. g. in schizophrenia might be related to HVH 1 activations (Libíková *et al.*, 1977).

In connection with our mentally healthy controls, who were not healthy in general, we would like to quote the paper by Bruhn (1974) who stressed the worrying defining of human "health".

References

Ado, A. D. (1978): *Obshchaya Allergologiya*. Meditsina, Moscow.

Bruhn, J. G. (1974): The diagnosis of normality. *Texas Rep. Biol. Med.* **32**, 241—247.

Enders, J. F., Kane, L. W., Maris, E. P., and Stokes, J., Jr. (1946): Immunity in mumps. V. The correlation of the presence of dermal hypersensitivity and resistance to mumps. *J. exp. Med.* **84**, 341—364.

Fuller-Torrey, E., and Peterson, M. R. (1976): The viral hypothesis of schizophrenia. *Schizophrenia Bull.* **2**, 136—146.

Fuller-Torrey, E., Peterson, M. R., Brannon, W. L., Carpenter, W. T., Post, R. M., and Van Kammen, D. P. (1978): Immunoglobulins and viral antibodies in psychiatric patients. *Brit. J. Psychiat.* **132**, 342—348.

Hašková, V., Kašlík, J., Matl, I., and Matějíčková, M. (1977): Nový způsob stanovení cirkulujících immunokomplexů v lidských sérech. *Čas. Lék. čes.* **116**, 436—437.

Korneva, E. A. (1976): Attempts at neurohumoral modulation of the secondary immune response (in Russian), pp. 180—182. In N. P. Bekhtereva (Ed.): *Mekhanismy Modulatsii Pamyati*. Nauka, Leningrad.

Kutinová, L., Vonka, V., and Řezáčová, D. (1977): Production and some properties of neutralizing antigens of herpes simplex virus. *Acta virol.* **21**, 189—197.

Kutinová, L., and Vonka, V. (1978): Determination of virus-specific antigens in extracts from herpes simplex virus infected cells by a ^{51}Cr-release inhibition test. *Ifect. Immun.* **20**, 587—591.

Kutinová, L., Šlichtová, V., and Vonka, V. (1979): Immunogenicity of subviral herpes simplex virus preparations. I. Formation of neutralizing antibodies in different animal species after administration of herpes simplex virus solubilized antigens. *Arch. Virol.* **61**, 141—174.

Leššo, J., Hána, L., and Matis, J. (1976): Reactions of immune sera against the nucleocapsid, envelope and whole herpes simplex virus type 1. *Acta virol.* **20**, 48—52.

Libíková, H., Pogády, J., Wiedermann, V., and Breier, Š. (1976): Prítomnosť protilátok proti vírusu herpes simplex typ 1 u osôb s psychickými poruchami a v kriminálnej populácii. *Čs. Psychiat.* **72**, 206—210.

Libíková, H., Stanček, D., Wiedermann, V., Hašto, J., and Breier, Š. (1977): Psychopharmaca and electroconvulsive therapy in relation to viral antibodies and interferon. Experimental and clinical study. *Arch. Immunol. Ther. exp.* **25**, 641—649.

Libíková, H., Breier, Š., Kočišová, M. Pogády, J., Stünzner, D., and Ujházyová, D. (1979*a*): Assay of interferon and viral antibodies in the cerebrospinal fluid in clinical neurology and psychiatry. *Acta biol. med. germ.* **38**, 879—893.

Libíková, H., Pogády, J., Rajčáni, J., Škodáček, I., Čiampor, F., and Kočišová, M. (1979*b*): Latent Herpesvirus hominis 1 in the central nervous system of psychotic patients. *Acta virol.* **23**, 231—239.

Oldstone, M. B. A., Dixon, F. J. (1976): Immunopathology of viral infections, p. 303. In P. A. Miescher and H. J. Müller-Eberhard: *Textbook of Immunopathology*, Grune and Stratton, New York, Sn Francisco, London.

Pepys, J. (1975): Skin testing. *Brit. J. Hosp. Med.* **1975**, 412—417.

Rajčáni, J., Sabó, A., and Blaškovič, D. (1969): Vergleichende Untersuchungen zur experimentellen Pathogenese des Herpes simplex-Virus bei der Maus. Intrazerebrale, intraperitoneale und orale Infektion der Säuglingsmaus. *Zbl. Bakt. ParasitKde I Abt.* **211**, 421.

Rimón, R., Halonen, P., Anttinen, E., and Evola, K. (1971): Complement fixing antibody to herpes simplex virus in patients with psychotic depression. *Dis. Nerv. Syst.* **32**, 8822—824.

Rimón, R., Halonen, P., Puhakka, P., Laitinen, L., Marttila, R., and Salmela, L. (1979): Immunoglobulin G antibodies to herpes simplex type 1 virus detected by radioimmunoassay in serum and cerebrospinal fluid of patients with schizophrenia. *J. clin. Psychiat.* **40**, 241—243.

Sequiera, L. W., Carrasco, L. H., Curry, A., Jennings, L. C., Lord, M. A., and Sutton, R. w. P. (1979): Detection of herpes simplex viral genome in brain tissue. *Lancet ii*, 609—612.

Škoda, R., Ivaničová, S., Jamrichová, O., and Sliepka, M. (1968): Die kutane Überempfindlichkeit der Schweine bei Aujeszkyscher Krankheit. *Arch. exp. Vet. Med.* **22**, 925—936.

Van Rooyen, C. E., and Rhodes, A. J. (1948): *Virus Diseases of Man.* Thomas Nelson and Sons, New York.

Walford, R. L. (1967): The general immunology of aging, p. 159. In B. L. Strehler (Ed.): *Advances in gerontological Research.* Academic Press, New York and London.