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Hepatitis B infection in institutionalized Down's syndrome inmates: a longitudinal study with five hepatitis B virus markers

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SUMMARY

A 3-year longitudinal survey in a residential institution for the mentally retarded was carried out to study the epidemiology of hepatitis B virus (HBV) and to elucidate the different responses which Down's syndrome (DS) and non-Down's (ND) subjects have to HBV infection. Sensitive tests for the HBV surface antigen and antibody (HBsAg and anti-HBs), core antibody (anti-HBc) and 'e' antigen and antibody (HBeAg and anti-HBe) were used. The HBsAg and anti-HBs content of positive sera was quantitated accurately.

All twenty-six chronic carriers of HBsAg possessed anti-HBc and 73% possessed HBeAg. The presence of HBeAg was correlated with abnormal liver function and high titres of HBsAg. The fifty-nine DS inmates possessing anti-HBs at the beginning of the study had significantly lower anti-HBs titres than the corresponding forty-nine ND subjects, but had a higher frequency of both anti-HBc and anti-HBe. Within both DS and ND groups the presence of anti-HBe was correlated with higher anti-HBs titres and within the ND group, high anti-HBs titres were also correlated with the presence of anti-HBc. Most inmates possessing HBV markers at the beginning of the study retained them for its duration.

Of the initially seronegative inmates, proportionately more DS (88%) than ND (54%) acquired HBV markers during the study; of these converters, proportionately more DS than ND (33% *vs* 10%) infections had chronic HBsAg carriage as the outcome. Most of these chronic HBsAg cases also acquired persistent HBeAg. In those seronegatives converting to anti-HBs, anti-HBc and anti-HBe tended to be more frequent in DS than ND groups, and patients with anti-HBe possessed higher anti-HBs titres than those without anti-HBe. These findings were similar to those seen in those inmates positive for anti-HBs at the beginning of the study (the anti-HBs group). However, unlike the anti-HBs group, the peak anti-HBs titres achieved after primary HBV infection (seroconversion) tended to be higher in the DS than in the ND group. The latter results are interpreted as indicating that a deficient humoral response in DS inmates is unlikely to be responsible for the high rates of chronic HBsAg carriage so often seen in these subjects.

INTRODUCTION

Chronic hepatitis B virus (HBV) infections, as judged by the persistence of hepatitis B surface

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antigen (HBsAg), occur more frequently in institutionalized Down's syndrome (DS) inmates than in non-Down's (ND) inmates (Blumberg *et al.*, 1967). Deficiences in both humoral and cellular aspects of DS patients have been suggested as being responsible (Sutnick, London, & Blumberg, 1969; Sutnick, 1974), but the underlying mechanisms remain obscure. A recent study in Sydney (Boughton *et al.*, 1976) showed that institutionalized DS inmates who had eliminated HBsAg and developed antibody to it (anti-HBs) had a geometric mean titre about six-fold lower than corresponding ND inmates. Further studies comparing DS and ND antibody responses to seven other microbial antigens (Hawkes, Boughton & Schroeter, 1978) showed that the apparent humoral deficit to HBsAg did not apply to these antigens.

It was thus unlikely that a general humoral deficit of DS inmates could be invoked for their lower anti-HBs titres or for their predisposition to chronic HBV infection.

This paper relates an intensive longitudinal study in a moderately sized institution for the mentally retarded in Sydney. HBV infections were monitored quantitatively over a 3-year period for HBsAg and anti-HBs in the hope of clarifying the matters mentioned above. In addition, sensitive tests for the other HBV markers, core antibody (anti-HBc), 'e' antigen (HBeAg) and 'e' antibody (anti-HBe) were used. It was thought that the nature of the apparently anti-HBs-specific deficit in DS inmates and possibly other facets of HBV epidemiology might be elucidated by relating the presence and titre of HBsAg and anti-HBs to the incidence of the other HBV markers, both in patients positive for these at the initiation of the study and those patients acquiring them during its course.

MATERIALS AND METHODS

Study group. This consisted of the inmates of the residential institution for the mentally retarded in Sydney previously described in detail (Boughton *et al.*, 1976). Briefly, there were 116 DS and ninety-one ND inmates, the groups being roughly equivalent in age, sex and duration of institutional stay. On the basis of the HBsAg and anti-HBs status of the first serum sample, inmates were classified at the commencement of the study as having chronic antigenaemia, antibody (anti-HBs group), or neither. This latter group was divided further into those acquiring HBV during the study (converters) and those who at no time during the study exhibited HBsAg or anti-HBs (seronegative group) (Table 1). Comparisons of the frequency of anti-HBc, HBeAg and anti-HBe were made with reference to the four groups mentioned above (chronic antigenaemics, anti-HBs, converters and seronegatives).

Duration of study. The majority of inmates were bled every few months between October 1971 and November 1974. A few patients were surveyed for shorter periods around these dates. Sera were frozen at -20°C soon after collection and periodically thawed for testing.

Laboratory investigations. For anti-HBc, HBeAg, and anti-HBe, the first (usually December 1971) and last (usually November 1974) sample from each inmate was tested, using commercially available radioimmunoassay kits from Abbott Laboratories (CORAB™ for anti-HBc, ABBOTT-HBe™ for HBeAg and anti-HBe).

Table 1. Study population—grouped according to HBsAg or anti-HBs status at beginning of study

	Chronic HBsAg	Anti-HBs	Converters	Seronegative	Total
Down's syndrome (DS)	23	59	30*	4	116
Non-Down's (ND)	3	49	21	18	91

* One of these thirty seroconverters was a patient possessing low levels of anti-HBs in the first serum who nevertheless acquired chronic HBsAg during the study.

These tests are designed for diagnostic purposes to give a clear-cut qualitative positive or negative result. However, it was possible to gain an impression of the concentrations of the markers by comparison of counts given by test samples (S) with those given by negative controls (N). This is conventionally referred to as the S/N ratio. Each specimen collected during the study was tested for HBsAg and anti-HBs by the passive haemagglutination (PHA) technique (Vyas & Shulman, 1970). Where sera were negative, further tests were carried out by radioimmunoassay (AUSRIA II™ for HBsAg and AUSAB™ for anti-HBs [Abbott Laboratories]).

Titrations of HBsAg and anti-HBs were carried out by the PHA technique in at least one sample (usually the first) of all but five inmates. Titrations of sequential sera were also performed in about half the inmates who were positive for HBsAg or anti-HBs. In all titrations, conditions designed to minimize variability were adopted (Hawkes *et al.*, 1978). For estimation of geometric mean titres (GMT) of anti-HBs, a serum positive only by AUSAB™ was ascribed a titre of 5. (In our hands the PHA test has a sensitivity two-fold less than that of AUSAB™ and is used with a minimal dilution of 1:10.) Comparisons of GMT of anti-HBs in various groups of inmates were made with the Student's *t*-test.

Alanine aminotransferase (ALT) levels were determined on the majority of specimens collected.

RESULTS

Chronic HBsAg group

Table 2 indicates the frequency with which anti-HBc, HBeAg and anti-HBe were detected in chronically HBsAg-positive inmates. The disproportionate numbers in the DS and ND groups render comparisons between the two groups difficult, but there are several points about the chronic antigenaemic group as a whole which merit a brief comment.

Firstly, all HBsAg-positive inmates possessed anti-HBc. There was no obvious correlation between the titre of HBsAg and that of anti-HBc, as judged by S/N ratios. With one exception (a four-fold decline in HBsAg titre), levels of both remained stable throughout the study.

Most of the DS inmates who were chronic HBsAg carriers were also positive for HBeAg in the first sample (18/23, 78%); four of these had lost detectable HBeAg 3 years later.

The presence of HBeAg was associated with abnormal liver function and also with high titres of HBsAg. Thus, of the fourteen patients who were HBeAg-positive in both samples, all had mildly to moderately elevated ALT levels in several sequential samples, and the geometric mean HBsAg titre (first bleed) of this group was 6,900. Of the four DS inmates who had detectable HBeAg in 1971 but had lost it by 1974, all had elevated ALT levels in 1971, but the loss of HBeAg was accompanied in three by a marked decline in ALT levels. This group had an HBsAg GMT of 2,152 in the first

Table 2. Frequency of anti-HBc, HBeAg and anti-HBe in inmates chronically positive for HBsAg

		DS			ND		
HBV marker	Serum sample*	No. tested	No. positive	Per cent positive	No. tested	No. positive	Per cent positive
Anti-HBc	First	23	23	100	3	3	—
	Last	23	23	100	3	3	—
HBeAg	First	23	18	78	3	1	—
	Last	23	14	61	3	0	—
Anti-HBe	First	23	3	13	3	2	—
	Last	23	5	22	3	3	—

* Samples collected for most inmates in October 1971 (first) and November 1974 (last).

sample. Of the five HBsAg carriers who were HBeAg-negative (three positive for anti-HBe) only one had elevated ALT levels (mildly raised). The HBsAg GMT (first sample) of this group was only 735.

A similar trend was observed in the ND group in that the sole inmate who possessed HBeAg in 1971 had a raised ALT level, which had become normal by 1974, by which time the patient had become HBeAg-negative. Similarly, the two ND HBsAg carriers without HBeAg in 1971 and 1974 had normal liver function tests.

Finally, among chronic HBsAg carriers, there was no relationship between the frequency of either HBeAg or anti-HBe and such factors as age, sex or duration of residential stay.

Inmates possessing anti-HBs in initial serum sample (anti-HBs group)

None of these inmates (59 DS, 49 ND) possessed detectable HBsAg or HBeAg. With two exceptions (both DS with antibody detectable only by AUSAB™), inmates initially possessing anti-HBs remained seropositive throughout the study.

Previous work (Boughton *et al.*, 1976) had shown that the anti-HBs titre (GMT) of a similar group of DS inmates was significantly lower than that of the ND inmates. It was consequently of interest to see whether this difference in titre was associated with differing frequencies of anti-HBc and anti-HBe in DS and ND inmates. The frequency of these two markers in the 106 inmates with persistent anti-HBs is given in Table 3, which also shows the anti-HBs titres of the subgroups formed. The salient points are:

(1) A significantly higher proportion of DS than ND subjects possessed persistent anti-HBc (DS 96%, ND 80%; $P < 0{\cdot}02$); as judged by S/N ratios there was a tendency for DS inmates to have higher levels of anti-HBc than their ND counterparts.

(2) Taking the persistent anti-HBs group as a whole, persistent anti-HBe was more prevalent in DS inmates (39/57, 68%) than in ND inmates (22/49, 45%; $P < 0{\cdot}02$). However, there was no significant difference between DS and ND inmates in the proportion of persistent anti-HBc-positive individuals who also possessed persistent anti-HBe (DS 69%, ND 56%).

(3) The difference in anti-HBs GMT between DS and ND inmates (DS 64, ND 255; $P < 0{\cdot}005$) was not associated with differences in the frequencies of anti-HBc and anti-HBe in these groups. Thus for DS and ND inmates of equivalent anti-HBc and anti-HBe status, significant differences in the GMT of anti-HBs antibodies were still observed.

(4) Despite the above, there was a correlation between anti-HBs titres and the presence of other markers within DS and ND groups. Within the ND group, the thirty-nine anti-HBc-positive inmates had significantly higher anti-HBs titres than the ten without anti-HBc ($P < 0{\cdot}001$). (Unfortunately the number of DS anti-HBc-negative subjects was too small to allow this comparison to be made within the DS group.) Those individuals (DS and ND) whose sera contained anti-HBe had significantly higher anti-HBs titres than those whose sera did not contain anti-HBe ($P < 0{\cdot}001$).

(5) Most subjects remained consistent in their marker status and anti-HBs titre throughout the study. In those few instances where change in status did occur, changes in one marker could either occur independently of the others or in association with changes in another marker (see Table 3). The four inmates undergoing four-fold anti-HBs rises during the study showed no change in status of anti-HBc or anti-HBe.

Analysis was carried out to determine whether either the titre of anti-HBs, the frequency of anti-HBc or the frequency of anti-HBe was related to such factors as age, sex or duration of residential stay. It was found that no relationship existed other than the previously noted tendency of anti-HBs titres to diminish somewhat with advancing age and length of stay (Boughton *et al.*, 1976). Differences in age, sex and residential status of the two groups (DS and ND) could not account for the tendency of higher anti-HBs titres to be associated with the presence of anti-HBe in both DS and ND groups or for the bias of the DS group towards a higher frequency of anti-HBc and anti-HBe.

Finally, it was of some interest to compare the ALT levels of the anti-HBs group with those of the chronic HBsAg carriers. In contrast to the latter group, only a small proportion of both DS (7%) and ND (6%) patients with anti-HBs displayed any persistent elevation of ALT levels, and these

Table 3. Serological characteristics of anti-HBs group*

		Down's syndrome						Non-Down's			
Anti-HBc Status	First sample	Pos†				Pos		Pos		Neg	Neg
	Last sample	Pos 55/57 (96%)				Neg 2/57 (4%)		Pos 39/49 (80%)		Pos 3/49 (6%)	Neg 7/49 (14%)
Anti-HBe Status	First sample	Pos	Pos	Neg	Neg	Pos	Neg	Pos	Neg	Neg	Neg
	Last sample	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg
		38/55 (69%)	1/55 (2%)	2/55 (4%)	14/55 (25%)	1/2	1/2	22/39 (56%)	17/39 (44%)	3/3 (100%)	7/7 (100%)
Anti-HBs‡ GMT		107	20	10	31·2	1,280	5	1,543	189	5	8·2
								652		7·1	

The overall anti-HBs GMT of all the fifty-nine DS inmates including the two not shown (see below) was 64; that of the forty-nine ND inmates was 255.

* Two DS inmates who lost detectable anti-HBs between first and last samplings not shown. Both of these were positive only when tested by AUSAB technique.

† Pos = antibody detectable, neg = antibody undetectable.

‡ GMT = geometric mean titre of anti-HBs (based on first sample).

were as a rule mildly elevated only. The other interesting point of comparison concerned anti-HBc levels. Whereas all twenty-six HBsAg carriers (23 DS, 3 ND) possessed high anti-HBc levels (an arbitrary S/N ratio of 0·1 or less), only about two-thirds of the anti-HBc-positive inmates in the anti-HBs group possessed such high levels.

Seronegative inmates

Of the eighteen ND inmates who were negative for HBsAg and anti-HBs, none showed evidence of HBV infection as evidenced by the other markers. However, of the four DS inmates who had been assumed to be seronegative on the basis of surface antigen and antibody, one exhibited evidence of infection by possession of anti-HBc.

Inmates acquiring HBV during the study (converter group)

As reported previously (Boughton *et al.*, 1976), DS patients in this institution showed a greater tendency to become infected by HBV than did their ND counterparts, and a greater tendency if infected to become chronic HBsAg carriers. Thus thirty of thirty-four 'susceptibles' in the DS group (88%) acquired HBV during the study, and of these thirty, ten (33%) became chronic HBsAg carriers. The corresponding figures for the ND group were twenty-one out of thirty-nine 'susceptibles' becoming infected (54%) and two out of the twenty-one infected (10%) becoming chronic carriers of HBsAg. Not unexpectedly, most of the converters were young inmates. However, other than that, age (and sex) appeared to play no part in influencing either the clinical expression of HBV infection or the pattern of HBV markers resulting from such infection in either DS or ND patients.

(a) *Conversions to chronic HBsAg.* Of the ten DS and two ND subjects in this group, all developed anti-HBc and eleven of the twelve developed HBeAg; the twelfth patient developed anti-HBe. With one exception, these markers persisted to the end of the study, the period of observation varying from 5 months to 3 years. The exception, a DS patient, retained HBsAg for at least 3 years but lost detectable anti-HBc and HBeAg sometime between 15 months and 3 years after infection.

Ten of the twelve patients acquiring chronic HBsAg were tested frequently for liver function. All showed mildly or moderately elevated ALT levels around the time of their conversion, but only one, an ND patient, developed clinical hepatitis.

(b) *Conversions to anti-HBs.* Approximately equal numbers of DS (twenty of the thirty infected) and ND (nineteen of the twenty-one infected) converted to anti-HBs, some having transient HBsAg and HBeAg around the time of conversion. Although the relatively lengthy periods between sampling prevented accurate determination of the duration of antigenaemia, it was clear that DS seroconverters tended to retain detectable HBsAg for longer periods than did ND inmates before developing anti-HBs. A crude measure of this was seen in the number of sequential samplings in which HBsAg was detected in individuals prior to the appearance of anti-HBs. In the DS group, 40% of anti-HBs converters had more than one HBsAg-positive sample, 25% had one, and 35% had none. The corresponding figures for the ND group were 16%, 16% and 68%.

It was possible to determine anti-HBs titres (passive haemagglutination) in sequential post-conversion sera of seventeen out of twenty DS and seventeen out of nineteen ND converters to anti-HBs (Fig. 1a, b). For most patients, titres rose, rather slowly in some instances, to a peak, and remained at that level. However, three patients (2 DS, 1 ND) exhibited a significant (four-fold or greater) boost in antibody level from a previously stable titre, and a further four (2 DS, 2 ND) showed significant antibody decline during the observation period. The peak titre of anti-HBs attained appeared to be unrelated to whether the infection was clinical or subclinical. In the ND group there was some tendency for lower peak anti-HBs titres to be found in those inmates failing to develop anti-HBc and anti-HBe, but the small number of individuals concerned makes the significance of this uncertain.

With one exception, inmates who acquired anti-HBs, anti-HBc or anti-HBe retained these for the duration of the study. The frequencies of anti-HBc and anti-HBe in this group of patients and the anti-HBs titres of subgroups are presented in Table 4. The main points of interest are:

(1) As in the anti-HBs group (Table 3), both anti-HBc and anti-HBe were detected more frequently in DS than ND patients, although here the difference was not significant. Similarly, levels

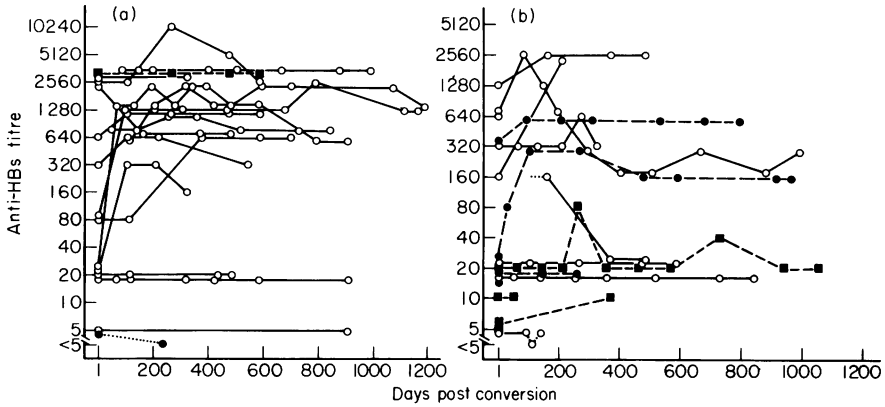

Fig 1. Anti-HBS development in subjects converting to antibody during study. (a) Down's, (b) non-Down's. The first positive serum after conversion is designated day 1. (o———o) Anti-HBc and anti-HBe-positive, (● - - - -●) anti-HBc-positive, anti-HBe-negative, (■ - - - -■) anti-HBc-negative, anti-HBe-negative. (. . . . .) Uncertain anti-HBs titre.

Table 4. Serological and clinical characteristics of inmates converting to anti-HBs during the study

	Down's syndrome		Non-Down's		
Anti-HBc status	Pos		Pos		Neg
	20/20 (100%)		15/19 (79%)		4/19 (21%)
Anti-HBe status	Pos	Neg	Pos	Neg	Neg
	17/20 (85%)	3/20 (15%)	11/15 (73%)	4/15 (27%)	4/4 (100%)
Clinical hepatitis	5	0*	1	0	0
Peak anti-HBs titre (GMT)	698 (16 patients)	5 (1 patient)	235 (9 patients)	95 (4 patients)	14 (4 patients)
	522		98		

* Two patients in this group showed biochemical dysfunction of liver at conversion.

of anti-HBc, as crudely judged by S/N ratios, tended to be greater in DS inmates. Patients who were negative for anti-HBc did not possess anti-HBe.

(2) Within both DS and ND groups, peak anti-HBs titres tended to be higher in inmates with anti-HBe than in those without it (DS, $P < 0{\cdot}05$; ND, $P < 0{\cdot}2$). In the ND group, inmates with anti-HBc had higher anti-HBs titres than those without ($P < 0{\cdot}05$). These are similar trends to those seen in the anti-HBs group (Table 3).

(3) Unexpectedly, the peak anti-HBs GMT of the DS group significantly exceeded that of the ND converters, taking the groups as a whole (DS 522, ND 98; $P < 0{\cdot}05$). For inmates of equivalent marker status, i.e. anti-HBc and anti-HBe-positive, a similar trend, not reaching significance, was seen (GMT: DS 698, ND 235). This is the reverse of the tendency in those inmates who were anti-HBs-positive at the inception of the study (Table 3).

(4) The clinical expression of HBV infection was not significantly higher in those converters to anti-HBs (6/39, 15%) than in those converting to chronic HBsAg (1/12). The clinical expression rate was not significantly higher in the DS group than in the ND group, and was not significantly associated with the presence of any particular combination of antibody markers.

Sequence of HBV markers in converters

Precise sequencing of marker development was precluded by the relatively wide spacing of the

sampling timetable. However, in general, anti-HBc or HBsAg were the first indicators of HBV infection. Less frequently, anti-HBs preceded anti-HBc. Neither HBeAg or anti-HBe were ever the first markers to appear.

DISCUSSION

From the standpoint of the general epidemiology of HBV in this institution, perhaps the most significant finding of this study was the high incidence of HBeAg in chronic HBsAg carriers (73%). This is somewhat higher than that found in similar studies (Tiku *et al.*, 1977; Gust, Dimitrakakis & Sharma, 1978, Hindman *et al.*, 1976), possibly because of the greater sensitivity of the test used here. The presence of HBeAg in serum has often been correlated with a high degree of infectivity (Okada *et al.*, 1976; Alter *et al.*, 1976; Shikata *et al.*, 1977), and the high proportion of such carriers in the present study is consistent with the rapid rate of HBV transmission observed within this institution. As reported in previous studies, HBeAg occurred only in HBsAg-positive carriers (Skinhøj, 1977) and was correlated highly with both the titre of HBsAg in serum (Shikata *et al.*, 1977; Couroucé-Pauty & Plancon, 1978) and with biochemical evidence of liver dysfunction (Tiku *et al.*, 1977; Couroucé-Pauty & Plancon, 1978; Hindman *et al.*, 1976.

All HBsAg carriers possessed anti-HBc and from perusal of S/N ratios it appeared that the HBsAg carriers tended to have higher anti-HBc titres than did those members of the anti-HBs group who also possessed anti-HBc (Hoofnagle *et al.*, 1974; Hoofnagle, Gerety & Barker, 1975). This presumably reflects the absence of continuing HBV replication in the anti-HBs group.

Within the anti-HBs inmates, there was a strong tendency for subjects possessing anti-HBe to have higher anti-HBs titres. Within the ND group, anti-HBs titres were also correlated with the presence of anti-HBc (there were insufficient anti-HBc negatives in the DS group to make this comparison). This relationship is not unexpected, in that all three markers are a product of HBV replication within an individual and it is not unlikely that subjects with the capacity to mount a good response to one viral antigen would respond well to the others. A similar relationship between anti-HBs titres and the other HBV antibodies was observed in inmates converting to anti-HBs during the study.

An important aspect of the study was to bring the newer tests, anti-HBc, HBeAg and anti-HBe, to bear upon the already observed differences in the responses to HBV infection of DS and ND inmates in this institution. These were: that DS inmates were more prone to HBV infection, were more likely to become chronic HBsAg carriers if so infected, and, on the basis of point surveys, more likely to have lower anti-HBS titres if positive for this antibody. The current longitudinal study extended these findings, allowing a tentative description of events to be put forward but unfortunately not in such a way as to give a unified explanation.

For reasons as yet unclear, DS inmates are more easily infected under conditions of apparent equal exposure than are ND inmates. After this primary infection most ND patients eliminate HBsAg normally, but DS inmates as a group have more difficulty in doing so. This is seen not only in the higher frequency of chronic HBsAg carriers in the DS group when compared with the ND group, but also in the longer periods of time for which HBsAg is carried by those DS inmates who eventually eliminate it and acquire anti-HBs. In the months following primary infection, such anti-HBs-positive DS subjects tend to have higher frequencies of anti-HBc and anti-HBe than do corresponding ND subjects, together with significantly higher anti-HBs titres. This is probably due to the greater antigenic stimulus experienced by DS subjects during their longer viraemia.

When sampled at longer intervals (years) after primary HBV infection (the anti-HBs group), the DS inmates still have significantly higher frequencies of anti-HBc and anti-HBe than do their ND counterparts, but have significantly lower titres of anti-HBs. The reason for the apparent anomaly is at present unknown. The most natural explanation would appear to lie in the difference between the response to a primary infection (converters) and that resulting from repeated exogenous HBV stimulus over a longer period of time by exposure within the institution. The fact that four-fold rises in anti-HBs titre were detected during the study is evidence that re-stimulation occurs. Perhaps the higher anti-HBs titres engendered by primary infection in the DS group make it unlikely that later re-infection occurs, whereas the relatively lower initial peak titre achieved by the ND group permits

re-infection and consequent anamnestic response. Further studies aimed at defining the immunoglobulin classes of specific anti-HBs in sequential sera of DS and ND inmates may be of assistance here.

The impetus of the study was the possibility that the low anti-HBs titres exhibited by the DS inmates might be reflective of the role of a poor humoral response in the establishment of the chronic HBV infection. One would expect that the critical stage in the establishment of the chronic state would be in the period around the primary, rather than the later, antibody response. As this response is apparently unimpaired in DS inmates, other immunological factors such as cellular immunity must be sought to explain the propensity of DS subjects to chronic HBsAg antigenaemia.

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