Immunological Studies of Heroin Addicts*

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SUMMARY **Combined clinical, biochemical and immunological studies were carrried out on 167 heroin addicts who were attending drug dependence treatment centres in and around Bangkok. One hundred and twelve of these were taking the drug by intravenous (I.V.) means and 55 by smoking it (i.e., they never injected heroin). Addicts comprising the smoking group had a significantly higher incidence of past respiratory illnesses although almost all of the addicts were quite healthy at the time they were being interviewed owing to the nature of the out-patient type clinic that they were attending. Asymptomatic (and probably sterile) pyuria was found in as high as 25.5 per cent of the smoking group and in 10.7 per cent of the I.V. group. Elevated serum glutamic oxaloacetic transaminase (SGOT) was found in 59.3 per cent of the I.V. group, a significantly higher level than the 26.9 per cent of the smoking group. The reason for the asymptomatic hepatic enzymitis is at present unknown, but it persisted even after the cessation of drug usage. It may represent a form of autoimmune chronic hepatitis. Contrary to the findings of other reports, we found no increased incidence of hepatitis B virus infection among Thai addicts. Circulating immune complexes (CIC) as measured by liquid-phase C1q-binding assay were positive in 40.4 per cent of the cases in the I.V. group, but only in 13.9 per cent of those in the smoking group ($P < 0.01$). The prevalence of CIC among the intravenous heroin users was confirmed by the higher incidence of rheumatoid factor and cryoglobulinaemia in the I.V. group. Such complexes probably can activate complement as evidenced by the prevalence of hypocomplementaemia in the I.V. group. However, the clinical significance of these immune complexes remains uncertain. They may play a role in the hepatic enzymitis and in the few cases of nephritis observed. Serum IgM levels were significantly elevated in the I.V. group, but the incidence of other auto-antibodies was not increased.**

The reason for these immunological dysfunctions among the intravenous heroin users remains conjectural. We postulate that parenterally administered heroin or its impurities may act as a polyclonal B-cell activator, resulting in hyper-IgM and the formation of circulating immune complexes, rheumatoid factor and cryoglobulins. This does not happen in the smoking group due to inadequate absorption or rapid inactivation via the respiratory tract. This hypothesis of heroin as a B-cell mitogen can be tested experimentally.

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Heroin addiction is one of the major socio-medical problems facing many nations around the world. Infectious complications are by far the most serious medical problems frequently encountered by intravenous heroin users; such complications include infective endocarditis, lung abscess and septicaemia.[1] In addition, non-infectious complications such as vasculitides,[2,3] nephropathy[4,5] and chronic hepatitis[6] have been reported occasionally.

The incidence of various biochemical and immunological abnormalities in a large group of otherwise asymptomatic heroin addicts has been occasionally reported such as the isolated reports of carrier states of HBsAg,[7] elevated liver enzymes,[8] hyper-IgM,[9] circulating immune complexes,[10] sterile pyuria[11] and auto-antibodies.[12] None of these abnormalities has ever been related to one another or correlated with other clinical findings.

We report here the biochemical and immunological changes in 167 asymptomatic Thai heroin addicts in relation to their preferred routes of heroin intake (i.e., intravenously or by smoking) and to their general medical health. The results indicate that the choice of route for heroin intake has implications with regard to different impacts on the biochemical and immunological changes in the addicts and these may play a role in the pathogenesis of some liver and renal complications seen in these addicts.

MATERIALS AND METHODS

Patients

One hundred and sixty-seven heroin addicts who were voluntarily

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attending drug dependence treatment centres in and around Bangkok were studied.[13] They were divided into two groups according to the route of heroin intake. The intravenous (I.V.) group, comprising 112 patients (108 males and 4 females) ranging in age from 17 to 64 years ($\bar{x}$ ± SD = 29.6 ± 9.0), was composed of addicts who regularly took heroin by I.V. injection. The smoking group, consisting of 55 patients (49 males and 6 females) ranging in age from 14 to 70 years ($\bar{x}$ ± SD = 35.7 ± 17.8), comprised addicts who regularly took heroin only by inhalation and/or ingestion, but never by injection. The drugs used by this latter group were heroin, opium and marijuana in 80 per cent, 16.4 per cent and 3.6 per cent of cases respectively.[13] The mean duration of heroin addiction of the I.V. group was 6.2 years (SD = 5.4) whereas that of the smoking group was 8.3 years (SD = 9.3). Patients who had been addicted for less than one month or who had already stopped taking the drug for over a week were not studied. The money spent on drug, an indirect indicator of the amount of drug being consumed, was not significantly different between the two groups of addicts (i.e., 135 ± 115 Baht per day in the I.V. group as compared to 107 ± 99 Baht in the smoking group).[13] Each addict was carefully examined and interviewed about any past medical problems occurring in the past two years, particularly those problems which occurred after addiction.

Laboratory studies

Following medical interviews and physical examination, urinalysis was performed and blood samples were obtained for renal and liver function tests as well as several immunological studies.

The immunological studies consisted of qualitative and quantitative detection of cryoglobulinaemia,[14] rheumatoid factor activity by latex fixation slide test[15] using human gamma globulin-coated latex particle (Hyland Diagnostic, Deerfield, Illinois, U.S.A.), haemolytic complement activity (CH50) according to the method of Mayer,[16] quantitative determination of C3 and C4 by radial immunodiffusion test using antisera and standard C3 and C4 as purchased from Hyland Diagnostic. Hepatitis B surface antigen (HBsAg) was detected by reverse passive haemagglutination test using hepatitis screening kits from Wellcome Research Laboratories, Backenham, England. Circulating immune complexes (CIC) were quantified by liquid-phase C1q-binding test as described by Zubler *et al.*[17] Serum IgG, IgA and IgM were measured by radial immunodiffusion test using standard antisera purchased from Hyland Diagnostic. Antibodies to nuclear antigens, smooth muscle antigens, mitochondria, reticulin and ribosome were done by indirect immunofluorescent test as previously described.[18]

Sera from 110 blood donors (108 males and 2 females) were used as normal controls for various laboratory tests as mentioned above. These were voluntary blood donors and to the best of our knolwedge, none took drug intravenously.

RESULTS

1. Circulating immune complexes (CIC)

Thirty-six of the 89 I.V. heroin addicts (40.4% of the total) had elevated CIC as determined by liquid-phase C1q-binding test, which was significantly higher than the incidence in the smoking group, i.e., five out of 36 cases or 13.9 per cent of the total ($p < 0.001$). The mean CIC level (% of C1q-binding) of the I.V. addicts as a group was also significantly higher than that of the smoking group; the CIC level of the latter goup was not significantly different from the normal controls (Fig. 1).

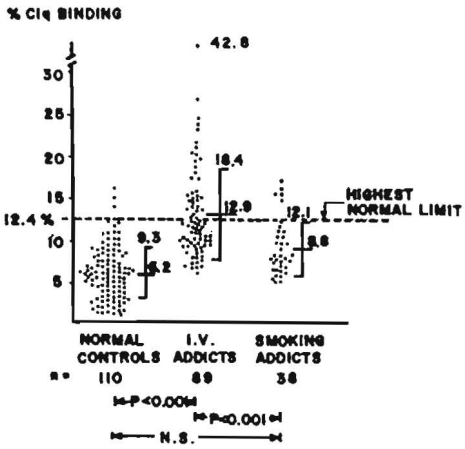

Fig. 1 Levels of circulating immune complexes in heroin addicts as determined by liquid-phase C1q binding assay. Mean and standard deviation of each group are represented by the vertical bars. C1q binding levels of more than 12.4% (mean + 2 s.d.) were considered abnormal.

2. Cryoglobulins

Cryoglobulins were detected in 27.3 per cent (30/110) of the I.V. addicts, slightly higher than that found in the smoking group (11/54 or 20.4% of the total). The levels of the cryoprecipitates in the two groups also were not significantly different, i.e., 0.140 ± 0.162 mg/ml in the I.V. group as compared with 0.051 ± 0.056 mg/ml in the smoking group. Nevertheless, the composition of the washed cryoprecipitates differed considerably in each of the two groups. Among the 23 cryoprecipitates from the I.V. group available for analysis, 17 were composed of both IgG and IgM, one each contained only IgG or IgM whereas no immunoglobulin could be identified in the remaining four. Analysis of 10 cryoglobulins from the smoking group revealed pure IgG in five of the subjects, IgG and IgA in one of them and no immunoglobulins in the other four. Rheumatoid factor activity could be detected in three cryoglobulins from the I.V. group, but not in those from the smoking group.

3. Complement levels

Total haemolytic complement activity (CH50) was low in 23 of the 112 I.V. addicts (20.5% of the total), significantly more frequent than the smoking group (i.e., 4 out of 55 or 7.3% of the total, $p < 0.05$). Among these, 10 of the I.V. group and one of the smoking group had CH50 lower than 10 units/ml, the lowest threshold level of our assay system (Fig. 2). In contrast with the CH50 level, the mean C3 level of the smoking addicts was significantly lower than that of the I.V. addicts which was in turn still significantly lower than that of the normal controls (Fig. 3). However, the mean C4 levels were not significantly different among the groups.

4. Hepatitis B surface antigen (HBsAg)

HBsAg was detected in 4.5 per cent (5/112) and 7.3 per cent (4/55) of the I.V. and smoking heroin addicts respectively, not significantly different from the 7.3 per cent (8/110) incidence in the normal controls.

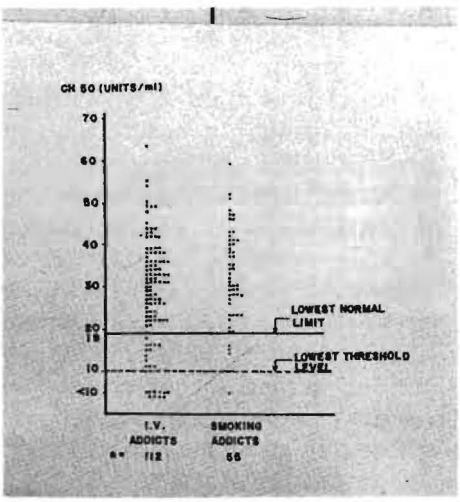

Fig. 2 Total haemolytic complement (CH50) levels in heroin addicts. Mean and standard deviation of CH50 in 110 normal controls were 28 ± 6 units/ml, Any CH50 levels of less than 19 units/ml were considered abnormal in our laboratory whereas 10 units/ml was the lowest CH50 level that could be detected in our assay system.[16]

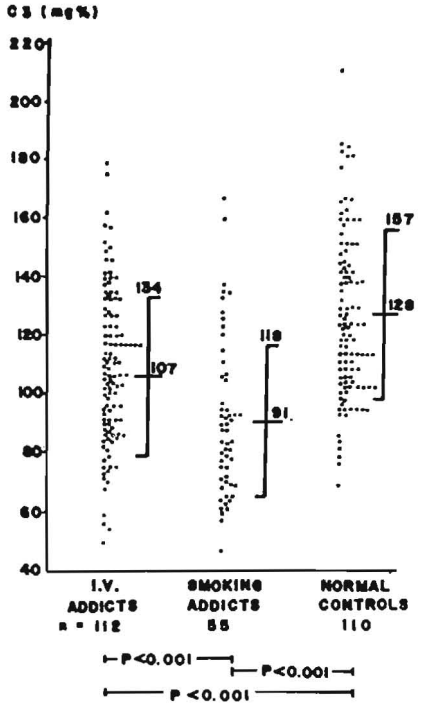

Fig. 3 C3 levels in heroin addicts. Mean and standard deviation of each group are represented by the vertical bars.

5. Immunoglobulin levels

Serum immunoglobulin levels were studied in 30 I.V. and 29 smoking heroin addicts. There was no significant difference in the levels of IgG and IgA among the groups. On the other hand, serum IgM levels of the I.V. addicts (200 ± 83 mg/dl) were significantly higher than those of the smoking group (106 ± 46 mg/dl; $p < 0.001$) or those of the normal controls (126 ± 72 mg/dl; $p < 0.001$).

6. Autoantibodies

Rheumatoid factor was detected in 9 per cent (10/112) and 1.8 per cent (1/55) of the I.V. and smoking addicts respectively, not significantly different from the 1.8 per cent (2/110) incidence in the normal controls. The incidence of autoantibodies to smooth muscle, reticulin, mitochondria and ribosome also was not increased in any group of the heroin addicts as compared with that of the normal controls.

7. Liver and renal function studies

Results of liver and renal function tests in both groups of heroin addicts are summarised in Table 1. Only four patients in the I.V. group had elevated serum bilirubin whereas 64 from the same group had elevated SGOT. Both the incidence of elevated SGOT and the mean SGOT level in the I.V. addicts, as a group, were significantly higher than in the smoking group ($p < 0.005$). In addition, although the incidence of elevated alkaline phosphatase in the I.V. group was not significantly higher than in the smoking group, the mean alkaline phosphatase level in the I.V. addicts, as a group, was significantly higher than it was in the smoking group ($p < 0.025$).

Similarly, although there was no significant difference in the incidence of azotaemia, glucosuria, albuminuria or microscopic haematuria between the two groups of addicts, the incidence of microscopic pyuria was significantly higher in the smoking group (i.e., 25.5% as compared with 10.7% in the I.V. group; $p < 0.025$) (Table 1).

8. Medical illness in heroin addicts

Each heroin addict was carefully interviewed concerning any significant medical illnesses during the two years prior to interview, particularly those illnesses which occurred after being addicted. The results are summarised in Table 2. It is worthy of note that the smoking addicts had a significantly higher incidence of past respiratory illnesses than did the I.V. addicts. Jaundice and well-diagnosed nephritis were equally distributed among both groups of addicts. Recurrent urticaria was found in three and one cases of addicts in the I.V. and the smoking groups respectively. In all of the three cases of recurrent urticaria in the I.V. group, the urticaria usually appeared a few minutes after the intravenous intake of the heroin and it gradually

Table 1 Incidence of abnormal liver and renal function tests in heroin addicts

Tests	Normal values	I.V. addicts	Smoking addicts	P value by Chi-square test comparing two groups of addicts
Liver function tests				
Total bilirubin	0.2 – 1.0 mg/dl	4/108* (3.7%)	0/52 (0%)	N.S.**
SGOT	< 20.5 u/l	64/108 (59.3%)	14/52 (26.9%)	< 0.005†
Alkaline phosphatase	20 – 48 u/l	10/108 (9.3%)	4/52 (7.7%)	N.S.††
Renal function tests				
BUN	15 – 38 mg/dl	0/102 (0%)	0/55 (0%)	N.S.
Creatinine	0.8 – 1.5 mg/dl	3/102 (2.9%)	1/55 (1.8%)	N.S.
Glucosuria	Neg-trace	0/112 (0%)	0/55 (0%)	N.S.
Albuminuria	Neg-trace	10/112 (8.9%)	1/55 (1.8%)	N.S.
Microscopic haematuria	⩽ 5 rbc/HD and female, not menstruating	5/112 (4.5%)	6/55 (10.9%)	N.S.
Microscopic pyuria	⩽ 5 wbc/HD	12/112 (10.7%)	14/55 (25.5%)	< 0.025

*number abnormal per number tested.
**no significant difference.
†mean ± SD of SGOT in the I.V. group = 34.1 ± 27.8 u/l as compared with 21.6 ± 14.7 u/l in the smoking group ($p < 0.005$).
††mean ± SD of alkaline phosphatase in the I.V. group = 33.4 ± 12.9 u/l as compared with 28.2 ± 13.6 u/l in the smoking group ($p < 0.025$)

Table 2 Past medical illnesses in heroin addicts

Illnesses	I.V. addicts (N = 112)	Smoking addicts (N = 55)	P value by Chi-square test
1. *Respiratory illnesses*	12 (10.7%)	14 (25.5%)	< 0.025
– Haemoptysis	5	5	
– Bronchial asthma	2	4	
– Chronic bronchitis	3	3	
– Pulmonary tuberculosis	2	3	
– pneumonia	0	1	
2. *Gastrointestinal illnesses*	12 (10.7%)	7 (12.7%)	N.S.*
– Peptic ulcer disease	6	2	
– Jaundice	3	4	
– Abdominal pain	2**	0	
– Liver abscess	1	0	
– Positive HBsAg	0	1	
3. *Recurrent urticaria*	3 (2.7%)	1 (1.8%)	N.S.
4. *Nephritis*	2 (1.8%)	1 (1.8%)	N.S.
5. *Miscellaneous*	7† (6.2%)	7†† (12.7%)	N.S.

*no significant difference
**One patient with chronic, intermittent abdominal pain of undetermined cause even before being addicted; the other patient developed intestinal gangrene two years after being addicted.
†One patient each with leprosy, degenerative arthritis, fixed drug eruption, postural dizzy spells, fractured leg, anaemia and recurrent abscess at injection sites.
††Three patients with degenerative arthritis, two patients with enteric fever and one patient each with gluteal abscess and car accident.

subsided within a few hours. This was particularly true with lower price heroin.

On physical examination, the abnormal findings detected in the I.V. group were right upper quadrant abdominal tenderness in three subjects, rhonchi in two of them, cellulitis around the injection site in two and one each with expiratory wheezing, cardiac murmur and jaundice. The abnormal findings detected in the smoking addicts were hypertension (diastolic blood pressure over 100 torr) in three of them, expiratory wheezing in two and one each with rhonchi, hepatomegaly and gluteal abscess.

DISCUSSION

Our combined clinical, biochemical and immunological studies of Thai heroin addicts have revealed certain differences among addicts according to their routes of heroin intake. Addicts who primarily took heroin by a parenteral route (the I.V. group) had a significantly

higher incidence and higher level of circulating immune complexes (CIC) than did the group which never took heroin parenterally (the smoking group). This may be due to the more direct and heavier antigenic challenge of the immune system by intravenous injection of heroin or the impurities in the heroin. Circulating immune complexes have been similarly described in 40 per cent of I.V. heroin addicts using Raji cell assay.[10] In addition, our study indicates that non-parenteral administration of heroin was not associated with an increased level of CIC. In many instances in our study, the presence of CIC was further supported by the simultaneous presence of cryoglobulins and rheumatoid factor, both of which were considered as the indirect evidence of circulating immune complexes.[19]

The I.V. addicts also had a significantly higher incidence of low CH50 than did the smoking addicts. This may reflect complement activation by the CIC present in I.V. addicts. However, although the mean C3 level in the I.V. group was significantly lower than that of the normal controls, it was significantly higher than that of the smoking group. The reason for such a discrepancy between the CH50 and C3 levels is unclear. It could not be explained as being a result of mishandling of the serum specimens because six out of seven addicts who initially had low CH50 continued to have a low level 6-9 months later. The mechanism of hypocomplementaemia in heroin addicts remains speculative. It may be due to complement activation via the immune complexes, i.e., classical pathway activation or via the alternate pathway similar to the case of radiocontrast media[20] especially with our finding that C4 levels were not decreased in any of the addicts. It would be of interest to measure the levels of C1q and factor B in the heroin addicts along with the measurements of C3, C4 and CH50. In addition, the hypocomplementaemia may also be due to decreased synthesis of complement components or due to increased complement catabolism as a result of heroin administration.

The clinical significance of the aforementioned immunological abnormalities in heroin addicts could not be assessed in our study due to the ambulatory type of treatment centres from which we recruited our addicts. Most of the addicts under study were in reasonably good health during the time of examination. In the I.V. group, there was no increased incidence of the immune complex-mediated diseases such as glomerulonephritis, arthritis or vasculitis. Nevertheless, both patients in the I.V. group who had a well-established history of nephritis within two years prior to the study were found to have abnormal urinalysis, hypocomplementaemia, rheumatoid factor, cryoglobulins and CIC. These findings indicated that both patients continued to have active immune complex-mediated nephritis. These abnormal findings persisted for up to six and eight months later when they returned for follow-up. It was unfortunate that permission for a kidney biopsy was not given by either patient. On the other hand, another patient with a past history of nephritis who belonged to the smoking group did not have any abnormal urinary or immunological findings as did those in the I.V. group. Therefore, although the clinical significance of CIC and hypocomplementaemia remains unclear in most heroin addicts, CIC and hypocomplementaemia may contribute to the immunopathogenesis of nephritis in some addicts.

Although only one addict in the I.V. group had clinical jaundice, 59.3 per cent and 26.9 per cent of the I.V. and smoking groups respectively had elevated SGOT. Our findings are consistent with those of Ortona *et al*[21] who found that 41 of their 82 I.V. heroin addicts (50%) had elevated SGOT. Ten of the 14 I.V. addicts whose initial SGOT levels were elevated were again found to have elevated SGOT when they returned for follow-up 6-9 months later. Seven of these 10 addicts reported complete abstinence from heroin usage. Our findings of persistent asymptomatic hepatic enzymitis months after cessation of drug abuse confirm those of previous reports.[6,8,22] The cause of such asymptomatic hepatic enzymitis in heroin addicts remains unknown. Its relation to viral hepatitis has been argued.[6] To our surprise, we did not find an increased incidence of the carrier state of HBsAg in our heroin addicts as reported by others.[7] This may be because Thai addicts are using more highly purified preparations of heroin as a result of easier access or it may be because they can purchase clean syringes and needles more easily than addicts in the U.S.A. In addition, the chronicity of abnormal liver enzymes, despite a cessation of drug abuse, may point to the process of auto-immune chronic hepatitis as its cause.

Microscopic pyuria was found in 10.7 per cent and 25.5 per cent of the I.V. and smoking addicts respectively. Our incidence is comparable to the 20 per cent incidence of asymptomatic sterile pyuria reported by Cherubin.[11] Although urine culture was not performed in our study, we believe that the pyuria in our patients was also sterile pyuria because none of our patients had urethral discharge or any symptoms of urinary tract infection, no significant bacteriuria was found and the pyuria was not a contamination of vaginal discharge since all the patients with pyuria but one were males. We did not know what was the cause of the pyuria although chronic interstitial nephritis was suspected. Renal biopsy may help to answer this question.

Our findings of high serum IgM levels in the I.V. heroin addicts support the earlier findings of Brown *et al*.[23] The smoking addicts had

normal serum IgM levels; this finding is similar to those of Blanck *et al.*[9] We postulate that heroin or the impurities in the heroin may act as a polyclonal B cell activator once introduced into the circulation. In I.V. addicts, it will then induce hyper-IgM, rheumatoid factor, cryoglobulins and CIC. This would also explain the high incidences of anti-smooth muscle antibodies and anti-lymphocyte antibodies in I.V. heroin addicts reported by Husby *et al.*[12] However, no increase in the incidence of various auto-antibodies was found in our study. The possibility of heroin as a polyclonal B cell activator is being tested in our laboratory.

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