when used several times daily (Lowbury and Lilly, 1960; Weatherall and Winner, 1963; Williams *et al.*, 1966), and some authors have questioned the effect of these preparations used only when personnel are on duty (Lowbury and Lilly, 1960; Weatherall and Winner, 1963). The present investigation, however, confirms the observation of Wilson (1970) that use only on duty effectively reduces the number of bacteria and the prevalence of staphylococci on the hands.

In previous studies Gram-negative bacilli have frequently been isolated from the hands of hospital personnel (Salzman *et al.*, 1968; Adler *et al.*, 1970). These bacteria, however, have usually been regarded as transient organisms which could easily be removed by washing with soap and water (Lowbury *et al.*, 1964; Brodie, 1965). In our study 18·8% of the personnel carried Gram-negative bacilli on their hands after washing thoroughly for one minute; the majority were carriers for more than two weeks, and some subjects were persistent carriers for months, perhaps years. The results of our study, therefore, strongly indicate that the Gram-negative bacilli should be regarded as frequent members of the resident flora.

Hexachlorophane is less effective against Gram-negative bacilli than Gram-positive organisms (Williams *et al.*, 1966), and the extensive use of these preparations for washing babies has been incriminated as the cause of increasing colonization and infection with Gram-negative bacilli among newborns (Forfar *et al.*, 1968; Light *et al.*, 1968). The results of the present study suggest that the routine use of these agents for hand disinfection by hospital personnel may promote colonization of the hands with Gram-negative bacilli, and it seems possible that the extensive use of hexachlorophane detergents may contribute to the recent increase in Gram-negative hospital infection (Bruun, 1970; Wilson, 1970). When staphylococcal infections represent a major problem, however, the danger of increasing the prevalence of Gram-negative bacilli should not prohibit the use of hexachlorophane detergents (Bruun, 1970).

In our study persistent carriage of Gram-negative bacilli was usually related to the presence of skin irritation or paronychia, and large numbers of bacilli were isolated from the skin lesions. Failure of antiseptics to reduce the number of bacteria during hand washing may have been due to the location of the bacteria deep in the skin layers. Nevertheless, during treatment of the paronychia with Onychophytex, which was applied to the lesions after hand washing, a marked reduction in the number of Gram-negative bacilli was shown. Search for skin lesions should therefore be included in the routine surveillance of hospital infections, and even minor lesions should be cultured and treated with a local application of effective antiseptics.

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Oral Glucose Tolerance and Hormonal Response in Heroin-dependent Males

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Summary

Tests on 12 heroin addicts showed that their response to a glucose load differed from that in normal controls. Though the fasting blood sugar was normal, the rise in blood glucose after a standard 50-g oral glucose tolerance test was delayed and the rise smaller than in the controls. The heroin addicts had high resting insulin levels and a delayed peak response to an oral glucose load, and their growth hormone response was also abnormal.

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Introduction

It is part of the folk-lore of narcotic addiction that an addict has a craving for sweet foods, and observation of the eating patterns of heroin-dependent patients attending a drug dependency treatment unit suggested that they have a preference for food containing a high proportion of carbohydrate.

It has also been part of the mythology of addiction that diabetes mellitus is more frequent among heroin addicts than other people. A survey of patients at the National Institute of Mental Health Addiction Research Centre, Lexington, U.S.A. (Sapira, 1968) showed that of 900 patients only one was diabetic, which suggests an incidence certainly no higher than that in the normal population. Chopra and Bose (1930), investigating an Indian belief that opium was beneficial for diabetes mellitus, found that in mild cases daily doses of 60-360 mg of opium produced a reduction of sugar in, or disappearance of sugar from, the urine. The blood sugar was not affected and it was suggested that one of the constituents of opium might influence the renal threshold for glucose. Desser and Arvin (1969) reported diabetic ketoacidosis occurring during acute heroin abstinence.

We report the results of some preliminary investigations on carbohydrate absorption and consequent hormonal release in 12 chronically heroin-dependent patients and 12 normal controls.

Subjects and Method

ADDICTS

All addicts were male patients who were taking heroin by intravenous injection and were attending the unit regularly for treatment. All were volunteers, and no attempt was made to select those who reported an increased liking for sweet foods. None had a family history of diabetes. Though, like most heroin addicts, these patients were known to take other drugs (usually hypnotics) at times, none admitted to having taken any illicit drugs in the 24 hours preceding the test. None showed any clinical evidence of recent illicit drug abuse nor had any evidence of infection either localized or general. All patients were asked about the size and time of their last heroin injection.

CONTROLS

Controls were selected from volunteer students and were all male. They were matched with the subjects on the basis of age, sex, and weight.

Both addicts and controls were weighed before the beginning of the test and asked about changes in food preference. Details of the subject's age, weight, and in the addicts, of heroin dosage are given in table I.

TABLE I—*Details of Age, Weight, and Heroin Intake where applicable in Subjects under Study*

	Age	Weight (kg)	Total Heroin Intake in 24 hr (mg)	Size of Last "fix" (mg)	Time Between "fix" and Test (min)	Resting Time Before Test (min)
Addicts:						
Range ..	18-27	60-71·5	20-220	10-60	8-126	20-95
Mean ..	22·75	65·6	60·8	22·5	54·7	39·6
Normals:						
Range ..	19-26	60-76	—	—	—	30-42
Mean ..	22	67·6	—	—	—	35·7

INVESTIGATIONS

Glucose Tolerance Test.—A standard 50-g oral glucose tolerance test was carried out on all subjects. The blood glucose estimation was carried out on an auto-analyser (Technicon) by the microferricyanide reduction method (Whichelow *et al.*, 1967) using a correction factor of 0·9 for estimation on plasma instead of whole blood. The presence of heroin as a reducing substance in the blood does not contribute greatly to results obtained by this method. Heroin in water at a concentration of 50 mg/100 ml gave a reduction equivalent to 15 mg glucose/100 ml. None of the patients were taking heroin in quantities to produce such a level in the blood. All tests were started between 8.00 and 10.00 hours. All subjects were requested to fast and not to smoke for 12 hours before the test. In one patient who had taken 30 mg of heroin 86 minutes before the test the microferricyanide results were checked by estimations using the glucose oxidase method. This yielded results which at the most were 3 mg/100 ml lower than the ferricyanide method. Further occasional checks on single samples from patients showed a similar close correspondence between the results found by the two methods.

Insulin Estimation.—This was a radioimmunoassay of the type described by Hales and Randle (1963a, 1963b).

Human Growth Hormone Estimation.—This estimation also was a radioimmunoassay based on Gallagher's (1972) method.

Cortisol Estimation.—Cortisol estimation was by the fluormetric method (Mattingley, 1962).

Liver Function Tests.—Standard liver function tests comprised the estimation of serum levels of bilirubin, total proteins and albumin and globulin, alkaline phosphatase, transaminases (SGOT and SGPT), thymol turbidity, thymol flocculation, and zinc sulphate turbidity.

Comparison of Group Means.—This was carried out using the standard Student's *t* test except in cases where a preliminary F test gave a statistically significant result suggesting that the two groups could not be considered as necessarily coming from one population. Under these conditions the approximate *t* test of Dixon and Massey (1951) was used (blood sugar at 90 minutes, insulin at 0 and 30 minutes, growth hormone at 0, 30, and 60 minutes, and insulin : glucose ratio at 60 minutes).

Results

Weight of Subjects.—The weights of addicts and normals, which are closely comparable, are shown in table I. All subjects fall within the range of average weight for adults (Society of Actuaries, 1959). Most were too young to compare with tables of desirable weights for adults.

Food Preferences.—Ten of the 12 patients reported an increased liking for sweet foods since they had become dependent on heroin, and two reported no change in their food preferences. No changes were reported by the controls.

Glucose Tolerance Test.—The mean blood sugars of the addicts in comparison with the means found in the normal male population are shown in table II, table III and fig. 1. The mean oral

TABLE II—*Results of Oral Glucose Tolerance Test in 12 Addicts under Study*

	Oral Glucose Tolerance Test (Mean ± S.E. of mean)				
	Fasting	30 min	60 min	90 min	120 min
Blood sugar (mg/100 ml) ..	79·9 ± 2·5	88·8 ± 2·5	95·2 ± 4·5	82·5 ± 6·3	80·1 ± 4·6
Plasma insulin (μU/ml)	22·2 ± 3·1	37·7 ± 2·5	47·7 ± 5·6	42·7 ± 4·8	40·8 ± 4·0
Plasma growth hormone (ng/ml) ..	20·4 ± 4·6	27·0 ± 7·7	17·9 ± 5·8	15·1 ± 6·9	13·2 ± 17·1
Plasma cortisol (μg/ml)	19·0 ± 2·5	15·3 ± 2·0	13·7 ± 1·5	12·9 ± 1·9	11·3 ± 1·7

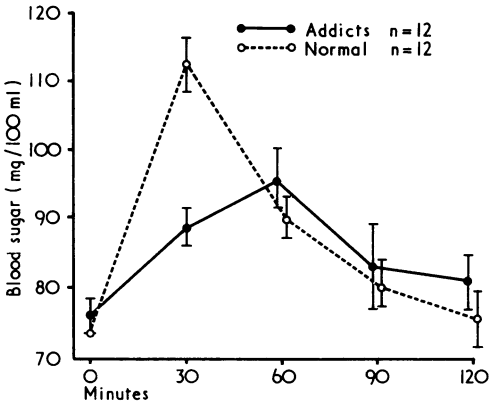

FIG. 1—Oral glucose tolerance test showing mean blood sugar in the two groups.

glucose tolerance curve obtained from the addict is clearly different to that found in the normals. The maximum rise of mean blood sugar is only 19·3 mg in the addicts compared with 39·1 mg in the normals, and the peak is delayed to 60 minutes in the addicts instead of occurring at 30 minutes. The difference between the patients and controls was significant at 30 minutes ($P = <0·001$) and the difference between the peak values of blood sugar in the two groups (at 30 minutes in the controls and at 60 minutes in patients) was also significant ($P = <0·01$). The addict group thus shows normal fasting blood sugar levels but has a significantly smaller and delayed rise in blood glucose in

response to a 50-g oral glucose load. The individual curves showed considerable variation from flat to a slow steady rise throughout the 120 minutes.

Insulin Response.—The means of the insulin responses of addicts and normals are shown in tables II and III and in fig. 2. Again there is a clear difference between the two groups.

TABLE III—*Results of Oral Glucose Tolerance Test in 12 Normal Subjects under Study*

	Oral Glucose Tolerance Test (Mean ± S.E. of mean)				
	Fasting	30 min	60 min	90 min	120 min
Blood sugar (mg/100 ml) ..	73·7 ± 1·9	112·8 ± 3·5	89·7 ± 3·3	80·2 ± 3·6	75·7 ± 4·0
Plasma insulin (μU/ml)	5·9 ± 0·5	33·4 ± 6·3	19·7 ± 3·7	17·2 ± 3·7	13·3 ± 2·5
Plasma growth hormone (ng/ml) ..	4·2 ± 2·4	4·0 ± 1·3	1·7 ± 0·3	1·1 ± 0·1	1·1 ± 0·0
Plasma cortisol (μg/ml)	24·2 ± 2·5	19·9 ± 2·0	20·2 ± 1·5	17·4 ± 1·9	16·9 ± 1·7

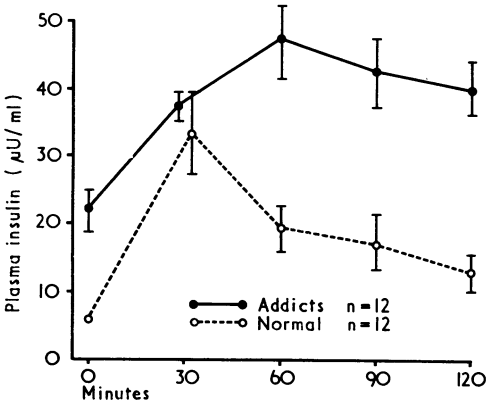

FIG. 2—Oral glucose tolerance test showing mean plasma insulin in the two groups.

The mean values were statistically significantly different at the following points: fasting ($P = <0·001$), 60 minutes ($P = <0·05$), 90 minutes ($P = <0·05$), and 120 minutes ($P = <0·01$). Comparison of the peak responses of the two groups (normals at 30 minutes and addicts at 60 minutes) showed no significant difference. The heroin addicts therefore show a high resting insulin with a delayed and raised (though not significantly so) peak response to oral glucose load, and also show a continuing high level of insulin remaining at 120 minutes 18·6 μU/ml above the mean fasting level compared with normals who were only 7·4 μU/ml above their fasting level.

Growth Hormone Response.—The means of the growth hormone responses of addicts and normals are shown in tables II and III and in fig. 3. There is a clear difference in the responses and mean values were significantly different at the following points: fasting ($P = <0·01$), 30 minutes ($P = <0·025$), 60 minutes ($P = <0·05$), and 120 minutes ($P = <0·05$). Though the 90 minutes means are comparable with the other points, significance was not reached because one subject gave a very much higher level at this time than during the remainder of the test. The addicts, in short, have a higher fasting growth hormone and continue to show a higher level throughout the test and do not show suppression of growth hormone in response to raised blood sugar.

Cortisol.—The means of the cortisol responses of the addicts and normals are shown in tables II and III and in fig. 4. The curves are very similar in level and shape (and approximate very much to the normal curves reported with a progressive drop throughout the day from a morning peak). None of the means shows a statistically significant difference.

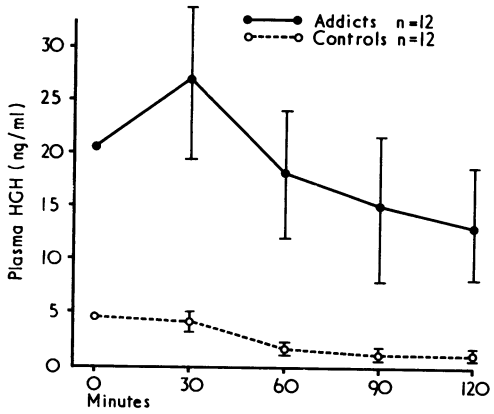

FIG. 3—Oral glucose tolerance test showing mean plasma human growth hormone (HGH) in the two groups.

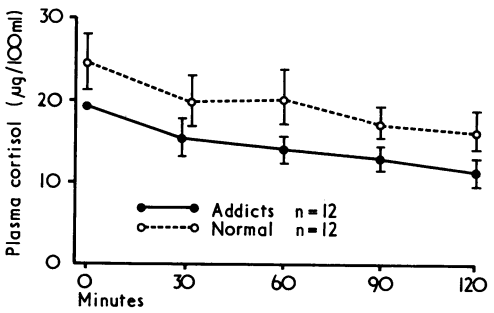

FIG. 4—Oral glucose tolerance test showing mean plasma cortisol in the two groups.

Liver Function Tests.—Both groups showed some deviation from the norms. Two normals had marginally low zinc sulphate turbidity and a further three had low serum globulins. Of the addicts, five showed completely normal results. In the remainder the commonest abnormality was a somewhat raised globulin (though maintaining a normal albumin/globulin ratio). The highest level was 4·6 g/100 ml with a normal upper limit of 3·5 g/100 ml. Two showed a slightly raised zinc sulphate turbidity and one a slightly raised serum alkaline phosphatase. Two showed raised transaminases, though the greatest change was 12 Frankel units/ml above the accepted upper level of normality. It is important to note that only two cases showed more than one abnormality.

Discussion

There are then three main differences between the groups: a low and delayed rise in blood sugar, a high insulin with a delayed rise, and a high and non-suppressing growth hormone. Either extraneous factors or some heroin-induced anomaly might account for the differences between the two groups.

Considering first "extraneous factors." All the tests were done on outpatients using, in the addict group, a notoriously unreliable population. In six addicts repeated "fasting" estimations were done and none showed a greater variation in blood sugar than 2-3 mg/100 ml. No fasting level in either group was higher than 92 mg/100 ml. In all it seems probable that the subjects were fasting when tested.

Neither the size of the daily dosage of narcotic, nor the size of the most recent "fix," nor the length of time since the last "fix" appear to have any obvious relation to the blood glucose curve.

Liver damage is reported both as resulting in an abnormal glucose tolerance test curve and to be associated with lack of suppression of growth hormone after glucose load. This, however, occurs only with severe hepatic dysfunction. While recognizing that liver disease can be present with normal liver function tests, the presence of liver dysfunction severe enough to cause these abnormalities seems unlikely, though a possibility to be investigated.

There remains the possibility that diamorphine has some effect on the absorption, metabolism, or excretion of glucose.

Several authors have reported the effects of single doses of morphine on blood glucose. It seems to be clear that a single dose of morphine may produce a transient hyperglycaemia both in humans (Holm 1923; Plant and Pierce, 1928) and in dogs (Borison *et al.*, 1962). However, this response disappears as dependence develops and may be replaced by a mild hypoglycaemia (Zahler, 1930).

Flat glucose tolerance test curves after narcotic administration have been reported (Holm, 1923; Light and Torrance, 1929; Tod, 1935), and Holm suggested that this may be due to delayed gastric emptying after morphine-induced pylorospasm. He reports normal glucose tolerance tests when intraduodenal glucose is given to dogs. The present blood sugar curves could be due to morphine-induced slow gastric emptying. These results are, however, from experiments on animals or non-addicted humans and many differences have been shown in the action of morphine between different species (Wilson and Schild, 1961) and between naive and chronically morphinized subjects (Zahler, 1930; Mule, 1969). Sapira (1968) reports that flat oral and intravenous glucose tolerance tests may continue to be found in addicts who have not taken narcotics for more than a year—a finding we have not been able to confirm (Ghodse and Reed, 1973). Walsh and his co-workers (Ng and Walsh, 1965; Walsh *et al.*, 1969) have shown in animal experiments that there is a relation between the presence of morphine and insulin activity in animal tissue and indeed that morphine may have an insulin-like action.

The results appear to be unlikely to be due to "stress" as this should be reflected in raised cortisol levels, whereas they remained normal in both groups. Indeed by this measure the addicts appear less stressed than normals.

INSULIN RESPONSE IN RELATION TO GLUCOSE RESPONSE

Variations in the relation between the degree of rise of insulin level above fasting and the degree of rise of glucose has been reported on several occasions (Seltzer *et al.*, 1967; Seltzer and Harris, 1968). Though Seltzer's most significant findings were present in intravenous glucose tolerance tests, similar findings were present in oral tests.

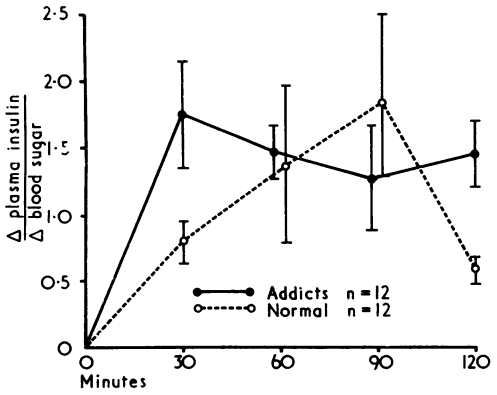

FIG. 5—Rise in plasma insulin compared with rise in blood sugar in the two groups (mean ± S.E. of mean).

This index of rise in plasma insulin compared with blood sugar in the addicted and normal group is shown in table IV and fig. 5.

TABLE IV—*Mean Insulin: Glucose Increment Ratios (± S.E. of mean) in both Groups*

	30 min	60 min	90 min	120 min
Addicts	1·8 ± 0·3	1·5 ± 0·2	1·4 ± 0·4	1·5 ± 0·3
Normals	0·8 ± 0·2	1·4 ± 0·6	1·9 ± 0·6	0·8 ± 0·1

At 30 minutes the addicts were responding to glucose challenge with a relatively greater output of insulin than were the normals, the remaining points not being significantly different.

Bleicher (1971) reviewed the factors which result in abnormal glucose tolerance. Inability of the B-cells to respond to a hyperglycaemic stimulus appears unlikely in view of the high or normal insulin : glucose increment ratios. Of the other factors mentioned in which there is insulin resistance and a heightened insulin response after glucose challenge, pregnancy (Bleicher *et al.*, 1964) does not apply, and the remainder are Cushing's syndrome, acromegaly, and the administration of exogenous growth hormone. Resemblance to Cushing's syndrome is ruled out by the normal cortisol levels and there remain two circumstances in which the primary abnormality is a high level of growth hormone.

There is then some degree of "insulin resistance" in the addict group, a high non-suppressing growth hormone, and a high insulin. It seems possible that morphine may promote growth hormone release—Cushman (1972) has shown anomalies of growth hormone in heroin addicts—and that the other abnormalities may be secondary to this.

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