

clinician of the significance to him and his patient of what has been discovered in the laboratory. Means must be found to bridge this gap.

Summary

The synthesis and exploitation of new therapeutic agents bring hazards as well as benefits to the patient. One hazard is actual or potential carcinogenic action. It is often not realized that the chemical structure of a compound rarely allows prediction of its carcinogenic properties, though it is to be hoped that such a relation will eventually be discovered. At present the only method of demonstrating carcinogenic activity is by laborious tests in animals, and even then the relevance of the results to man is uncertain.

The latent period of tumour induction is long, ranging in the human being from 5 to 40 years. There is no need for the carcinogen to be present during the whole of the latent period, so that a limited exposure in childhood may declare itself later in adult life. Little is known about the relation between the dose and tumour induction.

Carcinogenic therapeutic agents are here discussed as: (1) those of which the cancer-inducing properties were first demonstrated in man; (2) those of which the carcinogenic activity was first seen in animals but the compound had already been given to man; and (3) those which were withheld from man because their tumour-producing potential was discovered by animal experiment.

It is emphasized that laborious statistical investigation may be needed to uncover a relation between therapy and subsequent tumour induction, the treatment of ankylosing spondylitis by x-irradiation being cited as an example.

I hold the view that compounds which have been proved to induce tumours in man should not be administered to patients for any but the most exceptional clinical needs—for example, where the expectation of life is short and no other suitable drug is available. Drugs shown in the trial stage to be carcinogenic in animals should normally be withheld from man, in the knowledge that thereby valuable therapeutic agents may be lost. Drugs which have already proved their worth in therapy and which have subsequently been shown to induce tumours in

animals should be regarded with much suspicion and should in general be withheld from the young and from use as prophylactics. Thus an assessment must be made of the risks and of the benefits in each individual patient. This will be greatly helped by improved communication between the laboratory worker and the clinician.

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Six Cases of Acrylamide Poisoning

T. O. GARLAND,* M.D., D.P.H.; M. W. H. PATTERSON,* M.B., CH.B., B.SC.

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Early in February 1967 a 19-year-old youth (Case 1) was admitted to the Central Middlesex Hospital with severe peripheral neuropathy and dermatitis of the hands. The occupational health unit was asked to report on any toxic material that he might have contacted at work.

A director of the small factory where he was employed said that they had carefully reviewed all the materials he had handled and none of them could have poisoned him. He was held to be a rather dull lad, who virtually did only labouring work. He lodged with a local farmer, was a poor time-keeper, and by way of recreation spent much time in a local dance hall, which was under suspicion as a place where drugs were peddled.

In appearance the patient bore out this story. His ataxic walk and tendency to fall over almost emphasized it. His

mother had died when he was a child, and life had not been easy for him. He agreed that he was a bad time-keeper, especially lately. However, he denied that he had ever taken drugs, though he had been offered them at the dance hall, and added that lately he had given up smoking and drinking. He knew that he had been working with acrylamide, some of which came from the Cyanamid Co. of New Jersey, and some from Japan, and he told us that the bags from the U.S.A. had a warning label on them.

A further call was made to the factory chemist. He thought that acrylamide could be toxic and remembered having read in a booklet, issued by Cyanamid International, that it poisoned small mammals. The London headquarters of the Cyanamid Co. produced a paper on the toxicology of acrylamide by D. D. McCollister, F. Oyen, and V. K. Rowe, but assured us emphatically that they had no knowledge of any humans having suffered from it. McCollister's description of poisoned

* Central Middlesex Hospital, London N.W.10.

monkeys, however, made us feel fairly sure that the youth had been similarly poisoned.

The managing directors of two other firms making flocculators from acrylamide gave us names of employees whom they thought might have been further cases, and we visited seven factories where acrylamide was used. The cases described occurred in three of the four making flocculators.

A flocculator aids the separation of suspended solids from aqueous systems, which may be useful in mining, soil stabilization, the disposal of industrial wastes, and on any filtration or centrifugal process. There is a use for smaller quantities of acrylamide in the dyeing, photographic, plastic, paper, textile, ceramic, and paint industries.

Acrylamide

Acrylamide ($\text{CH}_2=\text{CHCONH}_2$), a white crystalline powder, is a vinyl monomer which exhibits the usual reactions of the amide group and will readily undergo polymerization and copolymerization. The polymer is non-toxic. It is when handling the monomer or during the process of polymerization that there is a hazard.

It should be noted, in passing, that a small paragraph in the Cyanamid booklet on the chemistry of acrylamide states: "Solutions of acrylamide can be stabilized when necessary by incorporation of cupric and ferrous salts or by organic inhibitors such as hydroquinone and *N*-phenyl- β -naphthylamine." This is a pointer to further care needed if these organic inhibitors are used.

Manufacturing a Flocculator.—The bare outline of the process is as follows: The bags of acrylamide powder are slit along the top with a knife and then emptied manually into a reactor vessel, either through the wide-open top or through a hopper. A catalyst, water, and other chemicals are added. As polymerization proceeds the mixture thickens, finally coming to the state of a gelatinous solid. At this point it is decanted into other vessels and subsequently washed and dried, cut up, and ground. When the polymer is ground up considerable fine dust is produced, but the heavier crystalline monomer does not appear to fly and cause a serious dust hazard. The finished product, sold as a flocculator, is in the form of a granulated solid.

Case Notes

We present these cases under some difficulties. Only one of them has been a patient in this hospital; the others live and work far from London. We have heard of them only through the assistance of their employers, and in regard to their clinical details have been helped by a number of doctors. We have ourselves examined all but one, Case 3, who was away on the Continent. Two are back at work quite well; two have returned—one with serious and the other with mild residual signs and symptoms; one we found still at work though severely poisoned; and one is still off work after eight months.

The situation clearly calls for a great deal more study and trailing, but the wide and growing use of acrylamide justifies an early warning of its dangers.

Case 1. Factory A

A 19-year-old labourer in a very small plant making flocculators first handled acrylamide in December 1966. He was seen in February 1967 complaining of severe muscular aching in the calves and buttocks and with a story of becoming increasingly unsteady on his legs. There was a weakness of his hands, noticed when controlling a bicycle, and finally his legs gave way abruptly on several occasions. The climax arrived in a dance hall, when, having collapsed on the floor, he could not get up again and an ambulance was called for.

The first sign he noticed was in January 1967, when his hands became excessively moist and the skin peeled off, about four weeks after the first contact with acrylamide. Shortly afterwards he was excessively tired and difficult to arouse in the morning, and then the presenting symptoms of weakness and loss of balance appeared. He had lost 7 lb. (3.2 kg.) since December 1966, but had had no diarrhoea.

On examination his palms were moist and peeling. He had a generalized coarse tremor, which had troubled him on two or three occasions in the previous few days. There was also a noticeable slurring of speech.

Neurological examination revealed normal cranial nerves, sluggish reflexes in the arms, and loss of knee and ankle jerks with absent plantar responses. Weakness and wasting of the small muscles of the hands was obvious, together with weakness of the wrist extensors (3/5 M.R.C. scale). Weakness of the dorsi and plantar flexors of the ankles was pronounced. Vibration sense was lost at the wrist and ankle, but there was no other sensory loss, and position sense was not impaired. There was marked truncal ataxia and a positive Romberg sign. C.S.F.: protein 40 mg./100 ml., 4 lymphocytes.

While in hospital his hands healed but the tendon reflexes in the arms disappeared. Otherwise there was little change in his condition, and he was discharged on 9 March.

On 29 April, three months after stopping work, he was still severely disabled and had lost a further 5 lb. (2.3 kg.). He had experienced further episodes of generalized uncontrollable shaking, worse in the upper half of the body. He had no diarrhoea or urinary symptoms. There was muscle-wasting, most pronounced in the anterior tibial compartment, and no return of power, but vibration sense was now intact. Tendon reflexes were absent and Romberg's sign was positive. By June he was much better, but still severely ataxic.

Case 2. Factory B

This man, aged 23, had been working with acrylamide for three months before the skin of his hands peeled. Two weeks later his finger-tips became numb and this numbness gradually crept up his hands. His grip became weak, he found shaving difficult, and he could not appreciate the temperature of his baby's bottle. Six weeks after the onset of symptoms his toes also became numb and his legs progressively weaker, until it became difficult to climb stairs and impossible to run. He stumbled frequently. He had no difficulty with his speech, no tingling, no impotence, no disturbance of micturition, no loss of appetite, and no disturbance of sleep. He worked until admission to hospital three months after his symptoms began.

On admission to hospital on 8 September 1965 there was an absence of tendon reflexes in arms and legs, loss of power in the small muscles of hands and feet, and anaesthesia of the fingers and toes to light touch and pinprick. Vibration sense was intact. C.S.F.: protein 29 mg./100 ml., cells nil.

He was discharged from hospital on 21 September and returned to work at the beginning of November, though there was still weakness of certain hand muscles. By March 1966 tendon reflexes had reappeared, and when we examined him on 17 April 1967, after he had been back working with acrylamide for some months, we found no abnormality whatever.

Case 3. Factory B

This man, aged 30, had been closely concerned with the previous patient (Case 2) developing the process for manufacturing flocculators. He knew his colleague's story and had had similar symptoms, but seems to have put up with them for four or five months before he consulted a neurologist on 10 March 1966.

He felt unbalanced at times when dancing, he had lost his sense of touch, and tended to drop cigarettes. These symptoms were more noticeable after taking alcohol. Generally he was very tired. The neurologist found arm and ankle jerks to be absent. Knee jerks were present though sluggish. There was slight loss of vibration and joint sense in the toes but no other sensory loss. The neurologist had also seen Case 2 and found the present patient much less seriously affected. Recovery was fairly quick and uneventful.

Case 4. Factory B

This man, aged 56, joined the factory in September 1966 and was immediately put to work charging the reactor vessel with acrylamide and decanting the gelling solution. After two months he became increasingly tired and very sleepy: "I would have a good night's sleep and then at the morning tea-break fall asleep again in the factory. The same thing would happen again at dinner-time."

He gave us a vivid description of falling down inside a tank at work before he went off sick, and being unable to get up again. About this time he could not be sure whether he was holding his cigarette or not, and was unaware of his fingers being burnt.

He first visited his doctor on 8 November 1966 complaining of having felt weak, drowsy, and unsteady on his feet for several weeks. Soon his speech became slurred, his general condition deteriorated, and he was admitted to hospital on November 15.

On examination the right arm and both legs seemed weak. Cranial nerves were normal and the only reflexes reported missing were the ankle jerks. There was no loss of vibration, touch, or pinpoint sense. The Romberg test was negative. A few days later the knee jerks had become very sluggish, but he quickly began to feel better and was discharged home on 30 November.

After he arrived home a new symptom developed, affecting his control of micturition. He found that he was wetting his pants, and when he went to micturate he passed only a small amount of urine, suggesting that his incontinence was an overflow phenomenon. He continued to find walking difficult—"My feet went platter platter all over the place"—and his speech was so slurred that his family had great difficulty in understanding what he said.

When we examined him on 17 April 1967 he was clearly much better in all respects, though still off work. His only complaint was a feeling of coldness and excessive sweating in the feet. "At one time I wore socks in bed to soak it up." Power in both arms and feet was good, but there was still some loss of sensation to pinprick in both hands and wrists. Knee jerks were still absent also.

Case 5. Factory B

On 17 April 1967, while watching a worker in this factory opening and emptying bags of monomer into the reactor vessel, we were struck by his ill appearance and with what difficulty he handled the knife. We therefore asked permission to examine him. He was aged 59 and had been working with acrylamide for more than a year. Six weeks previously he had been to his doctor because his feet felt dead and his grip was weak. He readily acknowledged that this was why he was so clumsy in opening the bags. "I can't get hold of the knife properly." He could no longer carry a bag of acrylamide, weighing 50 lb. (22.7 kg.), up a short flight of stairs and further complained of excessive sweating of the hands.

On examination his hand muscles were extremely weak, there was marked truncal ataxia, and Romberg's sign was strongly positive. All tendon reflexes were absent in arms and legs.

Case 6. Factory C

This man, aged 57, gave the impression of not being very bright and unlikely to observe rules for clean working. He had been exposed to acrylamide for only four to five weeks in June and July 1966.

On 23 July while returning home after his Saturday evening at the pub his legs suddenly gave way and he was assisted into his house, without much comment, but next day he felt "kind of light-headed," so took two days off. While at work on Wednesday, 27 July, his legs suddenly gave way again and he was sent home with strict instructions to see a doctor.

When referred to the neurological outpatient department polyneuritis was diagnosed. There were absent tendon reflexes, altered peripheral sensation, absent vibration sense, truncal ataxia, and a positive Romberg's sign. Sedimentation rate was 3 mm./hour (Westergren). Screening tests of urine porphyrins showed no excess of porphyrins or porphobilinogen. Wassermann reaction and venereal disease research laboratory test were negative. He was not admitted to hospital but continued to be seen as an outpatient.

At an examination on 13 January 1967 the biceps jerks were just present, whereas before they had been absent. Pinprick, light

touch, and joint sense were unimpaired in the lower limbs, but he could not appreciate vibration in the ankle. Romberg's test was positive. He was complaining of cramp in the legs and felt more dizzy.

By the end of February he was very much better. He could walk as well as ever before, and while the tingling in his hands had not quite gone the dizziness had disappeared, and Romberg's test was negative. He returned to work on 28 March. When we saw him on 17 April there was still slight wasting of the first right dorsal interosseous muscle and ankle jerks were absent. Power and sensation were normal in the legs and arms.

Discussion

The first paper on the toxicology of acrylamide was by Kuperman (1958), who worked solely with cats. It is clear from his second paragraph that these pharmacological studies were undertaken as a result of cases of accidental poisoning in humans in the U.S.A., but details have never been published. Kuperman found that the syndrome of acrylamide poisoning depended on the dose, the rate of administration, and the length of time during which it was administered. Severe tonic-clonic convulsions and other signs of a diffuse central excitation were produced by lethal doses. Repeated sublethal doses gave rise to a chronic and reversible intoxication, characterized by ataxia and postural and ataxic tremors. He found no histological alterations in neural tissue, and his experiments on decerebellate cats convinced him that the clinical evidence pointing to cerebellar asynergia could not be accepted as an explanation for the syndrome of chronic poisoning. He postulated finally that the primary neural locus of chronic intoxication is in the mesencephalic tegmentum.

A report on further extensive toxicological studies on rats, rabbits, guinea-pigs, cats, and monkeys was published by McCollister *et al.* (1964). They found that acrylamide was toxic whether absorbed cutaneously, orally, or parenterally. All species showed involvement of the nervous system, but the most impressive findings in relation to our cases were those in six monkeys.

Of these six monkeys, one was given 49 oral doses of acrylamide over a period of 69 days, at a level of 10 mg./kg./day. At 48 days there was some weakness of the hindquarters. At 69 days (total administered 690 mg./kg.) the hindquarters were extremely weak and the animal could not grip the mesh floor or climb the sides of its cage. At this point the animal was fed a normal diet and received no more acrylamide. After 94 days there was still no signs of recovery, but signs appeared after 101 days, and by the 123rd day it was well. This animal was allowed to survive and remained well long after.

A second animal died after heavier dosing, some time after administration of acrylamide had been stopped. In those fed less than 3 mg./kg./day for 363 days there were no signs of poisoning. McCollister *et al.* found no neurological tissue damage whatever in any of the affected animals, even in those intoxicated to the point of death.

Fullerton and Barnes (1966) published a paper which throws considerable light on the peripheral neuropathy that occurs in chronic acrylamide poisoning in rats, but they make no reference to the possibility of a central disturbance. In animals with severe clinical abnormalities, motor-nerve-conduction velocity in the fibres supplying the small muscles of the hind paw was reduced to approximately 80% of the velocity in the control animals. Histologically, degeneration of axis cylinders and myelin sheaths was found in peripheral nerves, affecting predominantly the distal parts of the largest fibres. When affected animals were no longer given acrylamide they recovered clinically, conduction velocity in the nerve fibres returned to normal, and there was histological evidence of regeneration of the nerve fibres. In rats that died shortly after being given sublethal doses repeated over 15 days, necropsy showed gross distension of the bladder.

Little has been published on human cases. Patty (1962) refers to a personal communication from H. H. Golz, and one is also mentioned by Fullerton and Barnes (1966). It appears from these that some men working with acrylamide in the U.S.A. developed numbness and tingling of fingers, followed by weakness of legs and unsteady gait, over 20 years ago. Presumably it was the knowledge of these that prompted the warning label on the Cyanamid Company's containers. There are two published reports on human cases in Japan. One describes intoxication in 10 out of 18 workers in a factory making acrylamide from acrylonitrile, but the description is incomplete in a number of respects (Fujita *et al.*, 1960). There is a further very brief report of a single case in a Japanese factory making flocculators (Anon., 1967). The author infers that there were other cases in the factory but gives no details.

A Canadian report (Auld and Bedwell, 1967) describes peripheral neuropathy in one man using acrylamide in a grouting process, stressing the excessive sweating of the extremities. We too found that many men working with acrylamide reported excessive sweating, erythema, and peeling of the hands, suggesting a direct reaction to the monomer, which would be readily soluble in sweat. In our cases working practice had allowed much skin contact and we concluded that poisoning had taken place via the skin rather than by inhalation of dust. In those factories we visited, where great care had been taken to avoid skin contact, there had been no cases.

The symptoms we have summarized in the Table correspond fairly closely with those described by Fujita *et al.*, who concluded that there was one lesion in the spinal cord, and another, on rather tenuous evidence, in the cerebellum. In the light of our cases and experiments on animals we consider that chronic acrylamide poisoning causes polyneuropathy and a midbrain lesion. The degree of motor and sensory impairment varied from case to case, a feature of polyneuropathy in general. The presence of ataxia, truncal in character, suggested a central disturbance, while the coarse generalized tremor seen in Case 1 and the dysarthria of Cases 1 and 4 indicated that this might be in the midbrain as postulated by Kuperman. This central disturbance explains the disproportionately severe ataxia associated with only minor sensory disturbances noted in Case 1 and the Canadian case.

Main Signs and Symptoms and Length of Exposure in the Six Cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age in years ..	19	23	30	56	59	57
Exposure in weeks ..	6	12	12	8	60	4
Hands peeling ..	x	x		x		
Increased sweating of feet and hands ..	x	x		x	x	
Fatigue, lethargy, and drowsiness ..	x		x	x	x	x
Muscle weakness ..	x	x	x	x	x	x
Muscle pain ..	x		x	x	x	x
Abnormal skin sensations ..		x		x	x	x
Sensory loss ..	x	x	x	x	x	x
Absent reflexes ..	x	x	x	x	x	x
Romberg's sign positive ..	x	x	x	x	x	x

In animal experiments it was possible to maintain a mild non-progressive state of intoxication if the dosage fell within a certain range (McCollister *et al.*, 1964; Fullerton and Barnes, 1966). This may be the reason why there have not been more cases of overt intoxication now that acrylamide is being handled in such large amounts. Midbrain involvement probably indicates more severe poisoning, as does deterioration after removal from exposure, seen in Cases 1 and 4. Case 1 had generalized tremors, a feature only of acute poisoning in animals, particularly the cat (Kuperman, 1958). Fullerton and Barnes (1966) found that young rats were less severely affected and recovered more readily than the older animals. This susceptibility in relation to age is not apparent in these human cases.

In two of the Japanese cases there was a suggestion of slight liver damage, and McCollister *et al.* found fatty necrosis of the

liver in one monkey and Kuperman found it in one cat. The work on animals does not shed any light on the bladder disturbance, which seems to be due to loss of sensation and muscle tone with resulting overflow incontinence.

Prevention

Prevention of poisoning should be easy. The warning label on the Cyanamid bags reads:

- Neurotoxic by skin contact, inhalation, or swallowing.
- Repeated contact may cause central nervous system disturbance.
- Avoid contact with skin or clothing.
- Do not breathe dust.
- Wash thoroughly after handling.
- Wash contaminated clothing before reuse.

These are simple and adequate instructions, but managerial skill can be severely tested in practice to ensure that they are carried out. We saw one man, in a minor supervisory position, dip his bare hand nonchalantly into a solution and hold it up dripping to see how gelling was proceeding. This was five minutes after we had been shown a list of rules for the workers laying down strict instructions how to carry out the process without skin contact. Neither the solid monomer nor a solution of the monomer should be handled with the bare hands or allowed to come into contact with the skin of the face or any other part of the body.

Acceptable and efficient protective clothing in the form of long polyvinylchloride gloves, light washable overalls, head covering, and face shield will protect the skin. If there is any suggestion of flying dust a light mask should be added, but it is very difficult to discipline workers over protective clothing, and masks are particularly disliked. The most important measure of all is to explain to those concerned, in simple language, exactly what the risk is. Acrylamide is not a deadly poison, but those handling it can be paralysed by absorbing much of it through the skin, and eventually more serious damage may occur in the brain. Straightforward instruction of this kind is commonly neglected. A word like "neurotoxic" on a warning label should not be used. Foremen did not know the meaning of it. The containers from Japan had no warning label on them at all, and clearly they should have had. Good washing facilities must be provided, and smoking or eating on the job forbidden. Besides careful explanation to the workers, it is absolutely necessary that management check working practice periodically. Medical monitoring once or twice a year is advisable where practice does not reflect good understanding and proper care.

Summary

Six cases of poisoning from handling the monomer acrylamide are described. All occurred during the process of polymerization of the monomer in the manufacture of flocculators. The mode of entry into the body appears to have been via the skin of the hands, though some ingestion of dust may also have occurred. The clinical picture is due to two distinct lesions in the nervous system—a peripheral neuropathy and a midbrain disturbance. The main signs and symptoms are numbness and paraesthesiae in the limbs; weakness, most marked in the lower limbs; increased sweating of the hands, with erythema and peeling of the palms; unsteadiness and loss of balance; and tiredness and lethargy without obvious personality change.

In addition, there may be generalized tremors, slurring of speech, weight loss, and some bladder disturbance.

Removal from exposure is followed by complete recovery in the less severely poisoned, but this may take from 2 to 12

months. With regard to the more severely poisoned, we are still in doubt whether complete recovery ever takes place.

It is a relatively easy hazard to contain. Awareness of the severely toxic nature of the substance on the part of the management and workers is the principal factor in prevention of acrylamide poisoning.

We wish first to thank the managements of the seven factories who allowed us to study their methods of using acrylamide. In particular we are grateful to those directors of factories making flocculators who unearthed cases among their own staff. They could so easily have behaved very much less helpfully.

We thank Dr. J. C. Phemister for his permission to publish Case 1 and for his advice throughout on the neurological aspects. We

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Fructose Intolerance

J. A. BLACK,* M.D., F.R.C.P.; K. SIMPSON,† M.D., M.R.C.P.

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Fructose intolerance is a genetically determined disorder in which the giving of fructose or fructose-containing sugars such as sucrose causes severe hypoglycaemia, while the continued absorption of small amounts of fructose results in fatty infiltration and fibrosis of the liver. The condition was first described by Chambers and Pratt (1956), and Froesch *et al.* (1957) in Zürich demonstrated the biochemical response in affected individuals to a dose of fructose or sucrose. Since then more than 40 cases have been described, and it is probable that fructose intolerance is at least as common as is galactose intolerance. In all except one family (Wolf *et al.*, 1959) the condition seems to have been inherited as an autosomal recessive.

This is a potentially fatal condition in infancy if untreated; in those infants who survive, hypoglycaemic symptoms may continue throughout childhood and even into adult life, and it is therefore equally important that the family doctor, the paediatrician, and the general physician should be aware of this easily treated disorder.

Case 1

The patient, a girl born on 19 March 1962, was the fourth child of healthy unrelated parents; birth weight 6 lb. 8 oz. (2.95 kg.). She was breast-fed for three days and later fed on various dried milks with the conventional additions of sucrose. On return home from the maternity hospital she began to vomit, lost weight, and became jaundiced. At the age of 1 month she was admitted to hospital. She was a pale, jaundiced baby with a blotchy face and a blood-stained nasal discharge. The abdomen was distended by ascites and by a moderately enlarged liver (two fingerbreadths below the costal margin).

Investigations.—Haemoglobin 8.8 g./100 ml. (61%); W.B.C. 27,000/cu. mm. (neutrophils 71%). Serum bilirubin 5.5 mg./100 ml. Serum alkaline phosphatase 22 units/100 ml.; thymol turbidity 1 unit; S.G.O.T. 140 units/100 ml.; S.G.P.T. 100 units/100 ml. Serum proteins 3.5%, with a lowering of albumin and β -globulin, and an elevated α_1 - and γ -globulin. Urine normal to routine examination.

One week after admission a laparotomy was done (Mr. H. H. Nixon). There was much ascitic fluid and the liver was greenish brown with a finely granular appearance. A piece of liver was removed; part of this was sent for routine histological examination and the rest was kept in a deep freeze. The histological report on the liver (Dr. Barbara Ockenden) was as follows: "There is intra-

lobular bile retention in the canaliculi, with widespread but patchy giant-cell transformation. There is a variable degree of sublobular cirrhosis. A little glycogen is present but there is no fatty change." A provisional diagnosis of giant-cell hepatitis was made, though galactosaemia was also considered, but was excluded by finding a normal activity of galactose-1-phosphate uridyl transferase in the infant's red cells.

After the laparotomy she improved. The urine at this time showed a gross amino-aciduria on two occasions with small quantities of galactose (50 and 12 mg./100 ml.) and traces (less than 5 mg./100 ml.) of glucose, sucrose, fructose, and lactose.

She was discharged at the age of 7 weeks weighing 8 lb. 5 oz. (3.77 kg.) but improvement was not maintained. At the age of 6 months she began to gain weight; by 8 months she weighed 14 lb. 10 oz. (6.63 kg.) and her liver was almost normal in size. Since her progress seemed much better than would have been expected of a child with a severe hepatitis the history was reviewed with her mother, who said that the baby had begun to thrive as soon as she had substituted glucose for sucrose in the feeds. She had done this because she had noticed that the patient's reaction to sucrose was similar to that of her first child (Case 2), whose history follows.

Case 2

This male child born on 26 September 1953 was breast-fed for one month and then changed to dried milk with the usual additions of sucrose. He did not take his feeds well and failed to gain weight on three different milks. A health visitor suggested that it was the sucrose which was upsetting him and advised the mother to use glucose. After this he gained weight but later developed a "screaming dislike" of sweet things, also carrots, peas, baked beans, fruit, and a variety of other foods.

A diagnosis of fructose intolerance in both children now seemed probable, and an oral fructose-tolerance test was performed by Dr. K. Simpson at Leicester Royal Infirmary (they had moved shortly after the diagnosis was suggested in London).

Comment

Case 1 was given 5 g. of fructose (0.5 g./kg. body weight). She vomited soon after her test dose and was sleepy for the rest of the day. A urine specimen during the test contained fructose. The response to the fructose was characteristic of fructose intolerance (Fig. 1). Case 2 was given 13 g. of fructose (0.5 g./kg. body weight). He became pale and drowsy and felt sick. The chemical changes in his blood were also typical of fructose intolerance.

* Consultant Paediatrician, Sheffield Children's Hospital.

† Consultant Paediatrician, Leicester Area.