Alcohol Intolerance in Neoplastic Disease

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It has been recognized in recent years that some patients with Hodgkin's disease have pain at the site of disease if they drink alcohol. A mouthful or two of beer or wine may be enough. Other vasodilators have no effect. James (1960) found 58 cases in the literature and suggested an incidence of 17% when patients are specially questioned. Symptoms other than pain (including cough, itching, flushing, and nausea) have been mentioned by only a few authors—for example, Zanes (1950) and Bichel (1959)—and have attracted little attention. Since the paper by James *et al.* (1957) isolated cases of alcohol pain in other neoplasms have been described, but have been thought to be very rare (Wanka, 1965).

This report concerns 155 patients with neoplastic disease who have shown alcoholic intolerance (Table I). It is suggested that such intolerance is both more common and more varied in its manifestations than has been supposed. The same small amount of alcohol capable of causing pain can produce other local effects, including bleeding; and can precipitate severe generalized symptoms so strange that the patient fears he will meet only disbelief and ridicule if he reports them. It is also shown that a sudden distaste for alcohol or a sharp lowering of threshold for its more normal effects may be equally significant; and that this type of intolerance, too, may return to normal after local irradiation of a small focus of disease.

TABLE I.—*Diagnosis in* 155 *Cases of Alcohol Intolerance*

Hodgkin's disease	60	Carcinoma of cervix	16
Reticulum-cell sarcoma	11	„ „ lung	9
Lymphosarcoma	11	„ „ bladder	6
Anaplastic lymphoid sarcoma	1	Squamous carcinoma of mouth, pharynx, or larynx	6
Reticular lymphoma (benign Hodgkin's)	1	Carcinoma of breast	4
		„ uterine body	3
Total in lymphoid group	84		

2 *cases of each of the following:* Carcinoma of kidney; thyroid; nasopharynx; vulva. Seminoma of testicle	10
1 *case each of the following:* Carcinoma of oesophagus; renal pelvis; ovary; penis. Sarcoma of uterus; Kaposi's sarcoma; sarcoma of prostate. Chronic myeloid leukaemia. Cervical-cord tumour (glioma?). Malignant retroperitoneal teratoma. Anaplastic retroperitoneal tumour. Bone metastases (primary site unknown). Granulosa-cell tumour of ovary. Tumour of glomus jugulare. Pituitary adenoma (acromegaly). Lymphangioma of tongue. Papilloma	17
Total in non-lymphoid group	71

Material and Methods

A total of 360 patients with Hodgkin's disease or other lymphoid tumour, seen between 1953 and 1965, and 700 patients with other neoplasms, mostly studied in 1964 and 1965, were asked about possible reactions to alcohol. Some were new patients. Others were attending radiotherapy or joint follow-up clinics long after successful treatment.

Bearing in mind the remarkable fact that the symptom of alcohol pain went apparently unrecognized until Hoster (1950) reported it, it was decided to record in detail any history of abnormal symptoms or a change in tolerance, whether or not it seemed at the time to make sense. Routine testing was not favoured. But some of those who had given up alcohol because of intolerance were asked if they would try it again. And selected patients were given repeated tests, often by means of alcohol capsules and dummy controls, in order to confirm their story of intolerance, to determine the smallest effective amount of alcohol, to discover the response to radiotherapy, to study the effect of certain drugs, and so on.

With a single exception (a young woman who claimed that alcohol made her cough) no test was carried out without first presenting the problem to the patient as research, for which he could volunteer or not as he pleased. If he seemed doubtful the matter was not pressed, and many tests were reluctantly modified or abandoned, though the patient had not withdrawn consent, because it did not seem right to carry them through to a convincing conclusion.

Some suggestive case histories that seemed at first doubtful, or hard to believe, became convincing as a result of finding similar cases, but it was thought best to reject 33 before arriving at the final figure of 155.

Alcohol Pain

Pain after taking alcohol was experienced by 79 patients (52 of them in the lymphoid group). Words like "terrible," "violent," and "agonizing" were used by a number of patients; and there were also references to the pain being strange or hard to describe and having a quality unlike any pain previously experienced. Many regular drinkers gave up alcohol completely and dared not resume it. Five men with Hodgkin's disease whose pain was not so severe described how they took prophylactic analgesic tablets before drinking.

Peripheral lymph-node enlargement (neck, axilla, or groin) was the site of pain in 14 patients with Hodgkin's disease and in one with a squamous carcinoma of the nasopharynx. Bone deposits gave rise to pain in eight lymphoid tumours, while seven patients (five Hodgkin's disease) had back pain without evidence of bone involvement, and four others (two Hodgkin's disease, two carcinoma) had pain associated with cranial or peripheral nerve involvement.

Abdominal pain was experienced by 19 patients (11 in the lymphoid group), in all of whom it was judged to be quite outside any "normal" upset due to alcohol. It occurred in the suprapubic region in three patients with carcinoma of the cervix and in three with carcinoma of the bladder, in two of whom there was also extreme urgency after very small amounts of alcohol. A patient with seminoma of the testicle and another with carcinoma of cervix had central abdominal pain, probably arising in secondary lymph nodes.

Chest pain occurred in 22 patients (19 in the lymphoid group). In 14 it was retrosternal, and in some of these it at first sight resembled severe dyspeptic heartburn a few minutes after swallowing alcohol. But in at least nine cases there was clear evidence of mediastinal disease and none of any involvement below the diaphragm. And in seven patients mediastinal irradiation abolished it.

Other sites of pain included: the mouth (three cases of squamous-cell carcinoma, one lymphangioma of tongue), vulva (squamous-cell carcinoma), testicle (seminoma), and skin

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nodules (Hodgkin's disease, Kaposi's sarcoma, breast carcinoma, and papilloma).

Generalized alcohol pain, as reported by Conn (1957), was experienced by four patients with Hodgkin's disease. It was aching, throbbing, or influenza-like, involving the whole body and often associated with malaise or drowsiness. In three of these it was a very early symptom, followed by long survival (for 4, 7, and 10 years). The same type of alcohol pain, but confined to the lower trunk and thighs, was experienced by a 37-year-old woman for 18 months before the diagnosis of a stage I carcinoma of the cervix.

Alcohol Bleeding

Bleeding from the site of disease after drinking alcohol occurred in 14 patients: 1 with Hodgkin's disease, 11 with non-lymphoid malignant tumours at various sites, and 2 with benign tumours (papilloma and lymphangioma). Alcohol tests in hospital confirmed the association in three cases. In the others the only evidence was the history given by the patient. But such histories can be extremely convincing.

Example 1.—A soldier aged 21 began to cough blood almost every day and noticed that it seemed to occur only after taking alcohol. If he missed an evening's drinking through being on guard duty it did not happen. During 14 days' detention for being absent without leave he coughed blood only once. This was when he was made to help clean up the sergeants' mess after a dance and found some unfinished beer. Thoracotomy seven months later showed Hodgkin's disease involving the lung.

Example 2.—A man aged 53, a heavy drinker, presented with a raised ulcerated lesion of the suprapubic skin 3 cm. in diameter. Clinically it looked malignant, but it proved to be a papilloma of the condyloma acuminatum variety. Tests demonstrated that half an ounce (15 ml.) or more of brandy was consistently followed by local pain and bleeding, the extent of which was roughly proportional to the dose of brandy. The vasodilator inositol nicotinate (Hexopal) was given twice in 400-mg. doses, but produced no pain on either occasion, though slight bleeding of doubtful significance occurred after the second dose. Prednisone was found to abolish both these alcohol effects, which did not return when prednisone was stopped.

Alcohol Attacks

The term "alcohol attacks" is suggested to describe the experiences of 18 patients, half of them with lymphoid tumours. All suffered acute distress of sudden onset, sometimes of a very bizarre kind and usually lasting an hour or more. No single symptom is common to all cases. Many patients had great difficulty in describing how they felt, but spoke of "horrible feelings," violent vomiting or headache, gasping for breath, sweating, giddiness, shivering, and sensations of being unable to speak or move, of heat, or of flushing. Sometimes diarrhoea followed.

One patient (carcinoma of cervix) described how within a few minutes of taking a spoonful of brandy she was violently sick and had a "terrible sensation in her arms and legs . . . like thousands of germs moving about inside her." Another (carcinoma of thyroid) had no nausea or vomiting at all, but was terrified by a sudden "flapping inside her head as if everything was loose." The exact words used by these two patients—both sensible women—are quoted in order to emphasize that abnormal alcohol symptoms often sound exaggerated and absurd, a fact of which the patients themselves are only too well aware and which partly accounts for their reluctance to report them.

In two cases capsules and dummy controls confirmed that a small amount of alcohol precipitated an attack. Of the seven men three said that they felt drunk after attacks. Women who felt ill or peculiar may have been speaking of the same thing.

Other Effects

Alcohol cough occurred in three patients with Hodgkin's disease involving the lung and in one with lung carcinoma. Shortness of breath occurred whenever alcohol was taken in a case of superior vena caval block due to lung carcinoma; and in two cases in the lymphoid group with enlarged mediastinal nodes. Abnormal alcohol flushing was described in association with alcohol pain and alcohol attacks; and it also occurred on its own in four patients (three lymphoid tumours, one well-differentiated thyroid carcinoma).

Other alcohol symptoms seen include sudden loss of consciousness; local sensory impairment (confirmed by capsule experiments); hiccup (after *small* amounts of alcohol, finally forcing a very embarrassed patient to give up drinking almost completely); pruritus (generalized in a patient with Hodgkin's disease; localized to the rectum in a young man with a sarcoma of the prostate); and deafness (in a patient with a tumour of the glomus jugulare, involving the middle ear).

Some General Points

Usually the pain or other symptom described above did not occur except after alcohol, but sometimes alcohol caused an existing symptom to become worse. A few patients said that "it did not happen every time." In 29 cases patients reported having to leave drinks unfinished. In several controlled tests 0.5 ml. of capsule alcohol had no effect, but 1 or 2 ml. produced pain. Two elderly women were distressed to find that they could no longer take even the smallest sip of communion wine at their church.

Most patients became aware of intolerance within 5 to 10 minutes of taking alcohol. Symptoms quite unrelated to the alimentary tract—for example, distant bone pain—were estimated by 16 patients to appear in less than two minutes (some said much less) from the first mouthful of alcohol. On the other hand, 13 patients (six in the lymphoid group) noticed nothing for at least half an hour. With some the interval was consistently as long as one to two hours.

Even when only a very small amount was taken the effect of the alcohol usually persisted for an hour or more. Durations of from three hours to three days were reported by 15 patients, only three of whom were in the lymphoid group. In most cases this was associated with heavy drinking on a Friday or Saturday night, the first clue to the association with alcohol being that certain symptoms were occurring only at week-ends.

In 59 cases alcohol intolerance began before diagnosis. In 20 patients it started more than a year before, often preceding all other symptoms by many months or even years. One man began to have suprapubic alcohol pain at least 15 years before he was found to have a bladder carcinoma. Others, some of them regular drinkers, experienced no intolerance until long after diagnosis.

After treatment normal tolerance often returned, as discussed below, even in the presence of other foci of disease. The type of tissue involved—for example, lymph-node or bone—does not explain this. In three patients with Hodgkin's disease extensive recurrence within an irradiated area was not accompanied by any recurrence of the alcohol pain previously felt in this area.

Some developed alcohol symptoms for the first time during or immediately after a course of radiotherapy; and in others it was found that treatment caused a "shift" from one alcohol pain to another or from one type of intolerance to another (Brewin, 1966).

Changes in Normal Tolerance

A sudden loss of desire for alcohol, dislike of its taste, or a considerable lowering of threshold for its normal intoxicating or "hangover" effects was noted by 68 patients, 46 of whom

never had any abnormal alcohol symptoms such as pain or bleeding. Certain gastro-intestinal effects (vomiting, epigastric discomfort, or diarrhoea) were also included here, when new to the patient but not quite outside "normal" limits. It might be thought that such effects would not be unexpected in a large unselected series of patients with neoplastic disease, and that they would be related to abdominal disease or to changes in general condition. But the evidence has turned out to be very much against such an explanation.

The change in tolerance often came early in the course of the disease; in 22 cases it preceded diagnosis. No correlation can be seen with sites affected or with subsequent spread of the disease. Patients with gross liver involvement, nausea, or anorexia were excluded; and 29 cases showed no evidence of abdominal disease of any kind, either at onset of the intolerance or for at least six months afterwards. Of the 68 patients 51 were regular drinkers, many of whom felt well and expressed great surprise at the sudden change in the way alcohol affected them.

In the final analysis the pattern of disease incidence in these patients was found to be strikingly similar to that seen in the "abnormal-symptom" group. For example, Hodgkin's disease, the other lymphoid tumours, and carcinoma of the cervix together make up 64% of the abnormal-symptom group (70/109) and 65% of the change-in-tolerance group (30/46). These three types of tumour account for only 41% of all neoplasms studied (437/1,060). Again, the proportion of patients with abnormal symptoms who also experienced one or more of the "changes in tolerance" was 20% (22/109), whereas the proportion of all other patients questioned was 5% (46/951). These differences are statistically highly significant ($P<0.01$).

Finally, changes in tolerance, as well as abnormal symptoms, sometimes responded dramatically to local irradiation of tumour tissue regardless of its site. This is discussed below.

Incidence

Table II shows the incidence of alcohol intolerance found in certain disorders (*a*) among all patients seen (except for the few who literally *never* took alcohol, who were excluded from the study), and (*b*) among "drinkers" (defined as patients unlikely to go more than two months without tasting alcohol). The higher incidence among "drinkers" is probably adequately explained by their greater chance of experiencing intolerance, and by the frequent difficulty of assessing the story of a patient who drinks only very occasionally. This view is supported by the finding that the incidence in *regular* drinkers (defined as those unlikely to go more than a week without tasting alcohol) was even higher—for example, 35 out of 58 regular drinkers with Hodgkin's disease; 10 out of 19 with carcinoma of the cervix—but that there was no further rise among daily or heavy week-end drinkers. In other words, if all patients were regular drinkers it looks as if intolerance would be revealed in nearly two-thirds of those with Hodgkin's disease and in half of those with carcinoma of cervix.

TABLE II.—*Incidence of Alcohol Intolerance in Certain Selected Conditions* (747 *Patients*)

Diagnosis	All Cases	"Drinkers" Only
Hodgkin's disease	31% (60/192)	45% (48/105)
Reticulum-cell sarcoma	20% (11/56)	44% (11/25)
Lymphosarcoma	16% (11/71)	30% (11/37)
Carcinoma of cervix	21% (16/77)	38% (14/37)
„ „ bladder	20% (6/30)	33% (6/18)
„ „ lung	14% (9/64)	22% (9/41)
Squamous carcinoma of mouth, pharynx, and larynx	6% (6/98)	10% (6/63)
Carcinoma of breast	2% (4/159)	5% (3/65)

"Drinkers" include all patients except (*a*) the "very occasional" group and (*b*) those whose normal drinking habit is not recorded. The latter comprise 15% of the total.

In considering whether these figures give a true picture the following points are relevant. Each patient in this series was questioned by the same observer. The manner of questioning is important and is referred to below. The patients were unselected, except that most of them were referred to a radiotherapist for opinion or treatment at some stage of their disease. It was realized from the start that a false impression of the incidence would result if any "negative" replies were not recorded or if colleagues were to invite me to see patients because of their alcohol symptoms. Not more than 6 cases out of 155 were seen because a history of intolerance had been elicited by a colleague. To set against these possible sources of exaggeration there is the fact that 33 suggestive cases were rejected, that some of the new patients recently questioned may be expected to develop alcohol intolerance in the future, and that a less cautious policy towards alcohol-testing of ill or nervous patients would probably reveal more cases.

The female sex preponderance in alcohol pain reported by James (1960) turns out to be equally true of intolerance in general and to apply to other lymphoid tumours as well as Hodgkin's. Of 81 male "drinkers" (see definition above) with Hodgkin's disease 32 (40%) showed intolerance. Of 24 female drinkers 16 (67%) showed intolerance. This is a significant difference ($\chi^2=5.5$; $P<0.025$). The same trend is seen in reticulum-cell sarcoma (6 out of 15 male drinkers, 5 out of 10 female) and in lymphosarcoma (4 out of 22 male drinkers, 7 out of 15 female). However, the incidence of intolerance in women drinkers with breast carcinoma is seen (Table II) to be very significantly lower ($P<0.01$) than in women drinkers with carcinoma of the cervix.

Response to Treatment of the Disease

In 60 patients there is evidence that treatment of a focus of disease resulted in disappearance of alcohol intolerance. The treatment was radiotherapy in 53 cases, a cytotoxic drug in four, and surgery in three. In most of the other patients (often because of a natural reluctance to risk any repetition of alcohol symptoms) there is no evidence one way or the other. In spite of wide variations in tumour sensitivity and in the dose of radiation given, no case has been seen where radiotherapy directed to the site of alcohol pain or other local symptom has clearly failed to abolish it. Moreover, in 12 patients who volunteered to take alcohol immediately before and again during radiotherapy it was found that the intolerance usually disappeared soon after treatment was started. Sometimes this was when the disease had apparently not regressed at all, let alone been eradicated.

Examples.—(1) A patient with Hodgkin's disease found that his alcohol pain was much less severe after 100 rads and was gone after 500 rads. (2) The very severe pelvic alcohol pain of a patient with carcinoma of the cervix was mild four days after radium was inserted and had completely gone when next tested two weeks later. (3) A heavy drinker who had been troubled by alcohol pain in an advanced ulcerated carcinoma at the angle of the mouth was quite free from it when test doses of up to 8 oz. (240 ml.) of brandy were given on the second day of a radium needle implant. (4) The severe alcohol pain of one patient in the lymphoid group no longer occurred after a test dose of only 3 mg. of intravenous nitrogen mustard.

Alcohol attacks (four cases), malaise accompanying pain (four cases), and generalized alcohol pain (two cases) have also been shown to disappear after local irradiation; while in 13 patients a strong feeling of distaste for alcohol, or a lowered threshold, has convincingly returned to normal, regardless of the type of tumour or the site irradiated.

Example.—A 56-year-old patient described how she suddenly "went right off alcohol" seven months before diagnosis of a stage I carcinoma of cervix. Having always previously enjoyed it (she confided that her singing in the local choir improved after three whiskies), she was very surprised, especially as she felt well and had

no gastro-intestinal symptoms. After radiotherapy she wrote, "So far I can enjoy a drink without any ill feelings; I do hope it lasts."

In some cases of "systemic" alcohol intolerance—for example, alcohol attacks or lowered threshold—of long standing the association of the intolerance with the tumour would have been in considerable doubt, in fact hard to believe, had not normal tolerance returned after radiotherapy.

Examples.—(1) A 66-year-old miner, with an "early" carcinoma of the vocal cord, described greatly increased "hangover" and diarrhoea after alcohol for 10 years before diagnosis. After radiotherapy to the larynx alcohol no longer affected him this way. His wife was specially interviewed and confirmed this (2) A patient aged 51 with a stage I carcinoma of cervix described vomiting, sometimes severe, on every occasion she had taken alcohol during a period of 11 years before diagnosis. Two weeks after radiotherapy she very cautiously tried some port sent to her as a gift and was surprised to find that it did not upset her in any way. Six months later she remained free from any intolerance.

It was never suggested to either of these patients that their alcohol tolerance might return to normal after radiotherapy.

Suppression by Non-cytotoxic Drugs

Relief of alcohol pain by antihistamines, first reported by Gros *et al.* (1953), was seen on several occasions. Complete suppression of alcohol pain and bleeding by prednisone has been described above. An equally convincing response to this drug was demonstrated in four other patients. A number of other patients had their alcohol intolerance abolished by a single prophylactic 100-mg. dose of phenylbutazone, a trial of which was suggested by the observation that a patient with Hodgkin's disease lost her alcohol flushing after phenylbutazone therapy for pruritus and fever. There were a few occasions when these drugs failed, but more often their effect was dramatic and was confirmed by comparison with the effect of dummy tablets. Patients with tumours in the non-lymphoid group responded as well as those in the lymphoid group. Experiments finally had to be abandoned in most of these patients because of fading of the alcohol effect until there was little or nothing left of it, though the total dose from these intermittent, mostly single dose, experiments was extremely small.

Example.—A man of 36, a regular drinker, had his first alcohol symptom two years after radiotherapy for an intramedullary tumour of the upper cervical cord (explored, but without biopsy; probably a glioma). Repeatedly, alcohol caused pain and stiffness in the neck and increased weakness of left arm and leg. It also made him much more drowsy and intoxicated than he would normally expect and gave him a bad "hangover" next morning. *All* these symptoms disappeared and his alcohol tolerance returned to normal if he took a single 5-mg. prednisone tablet one hour before drinking. Controlled experiments suggested that a little as 2.5 mg. was effective, whereas 1 mg. was relatively ineffective.

Discussion

If intolerance to a substance widely consumed all over the world since ancient times is anywhere near as common as Table II suggests, how is it that this is not generally recognized and that even the dramatic symptom of alcohol pain was apparently ignored until 1950? Two of the first patients in the present series said that in 1942 they began telling doctors of their severe alcohol pain. But the hospital records of these and other patients, often covering several admissions in great detail and including specific references to alcohol consumption, make no mention of it. Godden *et al.* (1956) and Bichel (1959) also examined large numbers of case histories of Hodgkin's disease and found nothing.

The explanation would appear to be twofold. First, there is always a tendency to reject any bizarre symptom that we do not understand; if the symptom occurs only after alcohol the temptation to do so is even stronger, because of traditional attitudes towards its effects. Several patients described how friends as well as doctors laughed at them. Four women said they were not believed by their husbands. Secondly, many patients are reluctant to speak of their alcohol intolerance unless given a sympathetic hearing and specific encouragement to do so. Most of those questioned said they had never before told anybody. Two women called in their doctors after severe alcohol attacks, but decided not to mention the alcohol they had drunk a few minutes before they were taken ill.

Experience shows that a mere awareness of these effects brings to light very few cases. Even direct questioning will often fail if it is not done very carefully. Some patients in this series were initially recorded as never having had any intolerance, but later admitted that this had been incorrect. Some of the most convincing cases occurred in women whose initial reply to questioning was that they never took alcohol. Such a reply may mean no more than the first systolic blood-pressure reading in a nervous patient. Most patients who "never drink" take alcohol occasionally. Some take it regularly, but in moderation. This the patient herself will often explain only a few minutes later, provided doctor and patient are alone, questions are tactfully phrased (to suit age, sex, and social background), and so long as the patient's image of herself as a total abstainer is treated with respect. The way is then clear for a discussion of possible alcohol intolerance.

Theoretical Implications

Sudden intense vasocongestion in the neoplastic tissue seems the most likely cause of the various local alcohol symptoms described. Swelling was reported by seven patients; 18 others spoke of throbbing, hardness, or tightness. The alcohol pain of one patient was much worse after biopsy. The fact that severe effects can occur within two minutes of swallowing a very small amount of alcohol suggests that there is no time for selective take-up, and that an extremely low concentration of alcohol is sufficient.

As regards the systemic effects (such as alcohol attacks, generalized flushing, or a lowering of the normal threshold to intoxication) there is a good deal of evidence to suggest that these symptoms, too, have a local unifocal origin in tumour tissue, presumably associated with the secretion of some substance into the blood-stream. It is difficult to see how else to explain the return to normal tolerance after local radiotherapy, regardless of the site of the tumour irradiated. It has not been thought justifiable to ask any patient to volunteer for "control" radiotherapy to a non-tumour-bearing area. But several cases have been seen where a local alcohol intolerance has persisted after irradiation of another focus of disease. In any case, no constitutional effects would normally be expected from the very localized irradiation that has abolished generalized alcohol symptoms.

The simultaneous onset of a local and a systemic effect, with disappearance of both after local irradiation, is also to be noted; together with the apparent association of systemic symptoms and lowered threshold with very early local pre-invasive changes, as judged by the presence of reversible alcohol intolerance for a number of years before the diagnosis of an "early" invasive neoplasm. The enzyme changes that have been reported in carcinoma-in-situ of the cervix (Bonham and Gibbs, 1962) might have some relevance here.

The fairly low dose of radiation that can abolish the alcohol effect (including other effects besides pain), and the lack of correlation with tumour radiosensitivity or cell type, may mean that the origin of the intolerance lies in tumour stromal cells rather than in the neoplastic cells themselves. Normal lymphocytes are known to be sensitive to radiation. James (1960) found eosinophils more numerous in cases of Hodgkin's disease showing alcohol pain. But when the histology of most of the non-lymphoid cases in the present series was reviewed (mainly

by Dr. J. S. Kennedy, of Glasgow Royal Infirmary) no common factor was detected. Eosinophils were unusually numerous in only one case, a carcinoma of cervix.

Except for the fact that pain has been a more common type of intolerance in the lymphoid group (and has tended to be more severe, though there have been notable exceptions), neither the histology nor the site of the tumour shows any obvious correlation with the type of alcohol intolerance experienced.

An impression that patients showing intolerance have a more favourable prognosis is of uncertain significance, since long survivors have a greater chance of experiencing it and have also been more readily available for questioning. But it could be that the higher incidence of alcohol intolerance in women with lymphoid tumours is connected with their better prognosis. It has been suggested that there may be a more efficient immune attack on auto-antigenic malignant cells in women (Burch, 1965).

The alcohol attacks observed seem in some ways like those that occur after alcohol when disulfiram (Antabuse) is given in the treatment of alcoholism or when the drinker has been exposed to cyanamide or certain other substances (Jacobsen, 1952). Albahary (1956) suggested that an enzyme having an effect like that of disulfiram might be responsible for alcohol pain in Hodgkin's disease. Raby (1949) described the case of an apparently normal subject who had symptoms after alcohol like those experienced by patients taking disulfiram and who showed the same increased acetaldehyde level. Fitzgerald *et al.* (1962), reporting alcohol symptoms of this kind in diabetics taking chlorpropamide, found no undue accumulation of acetaldehyde. Intramuscular injections of heptaldehyde may produce pain in the tumour in cases of breast carcinoma (Lawson *et al.*, 1956). Alcohol may precipitate the flushing of the carcinoid syndrome (Snow *et al.*, 1955). Loss of desire for alcohol associated with good appetite has been described in workers exposed to hydrogen sulphide (Kelly, 1949) or to tetraethyl lead (Walker and Boyd, 1952), and in alcoholics given metronidazole (Taylor, 1964).

Practical Applications

Because of the anxiety that might be caused, it is difficult not to have mixed feelings about symptoms that suggest to a patient the possibility of hidden neoplastic disease. But the onset of alcohol intolerance could lead to earlier diagnosis of carcinoma of the cervix and other curable tumours. At the same time it must be remembered that alcohol pain has occurred in this series in benign as well as malignant neoplasms ; and has been reported in a variety of non-neoplastic conditions, including osteomyelitis (Alexander, 1953), pancreatitis (Joske, 1955), sarcoidosis (Conn, 1957), simple fracture (Braun and Schnider, 1958), and in apparently normal subjects (Conn, 1957). The true incidence of alcohol intolerance in these and other conditions remains to be determined.

The persistence of alcohol intolerance after surgery or radiotherapy may mean that not all the disease has been covered by the treatment. If so, this could be a useful guide in management. But further study is needed to be sure of this.

Nothing has emerged to suggest that the taking of alcohol by these patients is either beneficial or harmful, though it may lead to very unpleasant symptoms for an hour or two.

Finally, many patients have in the past suffered much unnecessary discomfort, inconvenience, and anxiety because their alcohol intolerance was not recognized and treated. It is worth knowing that a return to normal tolerance is usually very easy to achieve by one or other of the methods described.

Conclusion

Alcohol pain in Hodgkin's disease is only a part of a much wider intolerance to alcohol, not uncommon in several neoplastic disorders and deserving further study in view of possible contributions to earlier diagnosis, to studies of the natural history and growth rate of tumours, and to fundamental biochemical and immunological problems.

Summary

After rejection of 33 doubtful cases, 155 cases of alcohol intolerance are presented ; 60 patients had Hodgkin's disease, 24 had other lymphoid disorders, 16 had carcinoma of the cervix, and 55 had a wide variety of other tumours, at least three of them benign. Alcohol caused pain at a site of disease in 79 cases, bleeding in 14, and severe generalized symptoms ("alcohol attacks") in 18. Other effects are described. Controlled capsule experiments have shown that 1 ml. of alcohol may be sufficient. Reasons are given to justify the inclusion of 46 patients showing only distaste for alcohol or a lowered threshold for its more normal effects.

It has been found that any of these forms of intolerance may (1) appear as a very early symptom of local neoplastic change ; (2) disappear after fairly small doses of radiotherapy to a focus of disease, quite insufficient to eradicate the latter ; and (3) be suppressed by small doses of cytotoxic drugs, antihistamines, corticosteroids, or phenylbutazone.

From the questioning of 360 patients with lymphoid tumours and 700 patients with other neoplasms it is suggested that alcohol intolerance is not uncommon in several apparently unrelated neoplastic conditions. In others typical cases occur, but only infrequently. In the lymphoid series intolerance is more common in women.

The need for careful questioning of the patient is stressed. Possible theoretical and practical implications are discussed.

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