muscle relaxants on patients in whom a carcinomatous neuropathy is suspected. The danger appears to be especially great in neuropathies due to bronchial carcinoma, and, where possible, bronchoscopy should be done under local anaesthesia alone. Although the majority of reported cases of carcinomatous neuropathy have been associated with bronchial carcinoma (17 of the 19 cases reported by Henson *et al.*, 1954), carcinoma at other sites may be responsible. Growths of the breast and ovary are already recognized as important in the production of neuropathy; in Case 3 a carcinoma of the sigmoid colon was present, while in Case 4 the neuropathy was due to a carcinoma of the prostate, although histological proof of this could not be obtained. These findings emphasize the need for a widespread search for a primary growth in suspected cases of carcinomatous neuropathy.

When prolonged states of neuromuscular block follow the use of one of the muscle relaxants, carcinomatous neuropathy should be considered as a possible explanation of the abnormal response to the drug.

Finally, patients with the different types of carcinomatous neuropathy must be investigated more intensively in the future, using combined clinical, biochemical, histochemical, and electromyographic methods of study, which may help to solve the problems of the metabolic abnormalities which are present. Since the time relations between the onset of the neuropathy and of the discovery of the carcinoma are so variable (Henson *et al.*, 1954) these investigations should be repeated at intervals, and where applicable particular attention should be given to any changes that may follow the removal of the carcinoma. Similar investigations may be helpful in other patients with unexplained neuromuscular disorders not associated with carcinoma.

Summary

Three patients with carcinomatous neuropathy but without overt myasthenia showed abnormal responses to muscle relaxants. Two other patients with carcinoma but without obvious neurological disorder showed similar abnormal sensitivity to these drugs.

The risks of using neuromuscular blocking agents in patients with carcinomatous neuropathy is discussed.

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A STUDY IN THE TRANSMISSION OF MATERNAL ANTIBODIES

BY

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The agent in the milk of mice which Bittner (1937) discovered to be concerned with the development of breast cancer in these animals has been the subject of intensive research, and much is now known about its chemical, physical, and biological properties. In all these it behaves like a virus, and it now seems probable that, given the appropriate murine, genetic, and hormonal background, the presence or absence of the mammary agent is responsible for the appearance, or the failure to appear, of mammary cancer in this species. The possibility that such a mechanism might operate in the development of human breast cancer has been widely canvassed.

Three methods of investigation have been undertaken to probe this important matter. In the first, human milk has been studied under the electron microscope (Passey and Dmochowski, 1951; Gross *et al.*, 1952) and particles have been observed microscopically resembling the particles in mouse's milk which have been identified with the mammary cancer agent. This finding, however, can do no more than suggest the possibility of a relation between the observation of such particles and the subsequent development of breast cancer. Indeed, even if a relation could be established, studies of this sort, whilst of the greatest theoretical interest, would not answer the

practical question of whether breast-feeding induced breast cancer in the offspring, because these particles, even if related to breast cancer, might equally well be transmitted through pathways other than the maternal milk.

The second method of study (Horne, 1950) is to take a group of patients with breast cancer whose mothers are still alive and to discover whether any of these patients were *not* put to the breast when they were infants. Horne's study strove to show that the proportion of babies not put to the breast amongst those who subsequently developed cancer of the breast was as high as in the general population. This finding, in distinction to the results of the first method, would argue against there being any factor in human breast milk tending to produce cancer of the breast. The fallacy in this line of research is that the memories of mothers, presumably now in their seventies and eighties, of whether or not they put their children to the breast even for a single feed fifty to sixty years before, must be grossly unreliable, and it is doubtful whether these findings are of any value.

The third method of approach to the problem is to trace the histories of infants who are known never to have received human breast milk and see whether subsequently they develop cancer of the breast in the same proportion as in the general population. This method has the great disadvantage that an answer cannot be forthcoming for another fifty years, but it is a study which is worth pursuing for the following reasons. Firstly, the answer, when it becomes available, will resolve without doubt whether breast-feeding has any relation to the development of human breast cancer; and, secondly, some interesting incidental questions may be studied in the meanwhile.

Present Investigation

The present paper is concerned with one of these incidental aspects in a group of female children who are being studied with the long-term object of determining the relationship of breast-feeding to breast cancer. It will first be necessary to describe how the groups of children or "panels" are collected and how disease occurring in one or other group is reported. In April, 1949, a letter appeared in the *British Medical Journal* (Atkins, 1949) asking for the co-operation of doctors in the collection of a panel of female babies who were known never to have received human milk. The declared purpose for collecting such a panel was to see whether they eventually developed cancer of the breast more or less frequently than the general population.

After the publication of this letter, and with the co-operation of a large number of doctors, it was possible to build up a panel of "milkless" babies, which is still growing steadily. It soon became obvious, however, that much more could be got out of this study than was originally planned, especially if a control panel was set up for babies who had been put to the breast. With each "milkless" baby, therefore, there was forwarded at the same time records of a breast-fed baby born in the same district during the same month, or in the preceding or subsequent month. In this way, within the larger group there has been established an élite of "milkless" babies each controlled by a matching baby born in the same district at approximately the same time.

The method of following the health history of these children is to send to the mother or guardian each year a form upon which she records any diseases or operations which the child has had during the previous year. The first form sent out asks for these details from birth. If no reply

is received, a letter is sent after three months and again after six months. If there is still no reply, the child's record is marked "lost" and the name and health card number is forwarded to the authorities at Somerset House, who have kindly undertaken to supply a copy of the death certificate of any children who are on the panel and who have died. In practice, only a very small proportion of parents have defaulted; indeed, we are inclined to be overwhelmed, though very pleasantly so, with photographs and anecdotes of our many members at the various milestones in their careers.

The data taken for the following analysis were derived from the records of 534 "milkless" and 534 breast-fed babies on the records at the end of May, 1957.

Study of the Two Groups

It was decided first to examine the incidence of gastro-enteritis, bronchitis with bronchopneumonia, and otitis media recorded for the two groups. These are set out in Table I. The similarity between the two groups in regard

TABLE I.—Incidence of Gastro-enteritis, Bronchitis, and Otitis Media

	"Milkless"	Breast-fed	t	P
Gastro-enteritis	22	21	—	—
Bronchitis and bronchopneumonia	60	49	1.13	.25
Otitis media	11	11	—	—

to the incidence of gastro-enteritis and otitis media is striking and requires no comment. The slightly increased incidence of bronchitis and bronchopneumonia amongst the "milkless" group (60/534:49/534) is statistically quite insignificant ($t=1.13$; $P=0.25$). So far as they go, these results bear out the findings of Stewart and Westropp (1953) that breast-feeding has no effect on the incidence of gastro-enteritis, bronchitis, or otitis media.

The second line of inquiry was into the incidence of the zymotic fevers—morbili, rubella, varicella, pertussis, and epidemic parotitis—in the two groups, with its special relevance to the possibility of the transmission of virus antibodies in the colostrum in humans. Table II shows that

TABLE II.—Incidence of the Zymotic Fevers

	"Milkless"	Breast-fed	t	P
Morbili	124	136	0.85	0.4
Rubella	30	37	0.93	0.35
Varicella	72	74	—	—
Pertussis	56	57	—	—
Epidemic parotitis	23	21	—	—

the incidence of the zymotic fevers in the two groups is strikingly similar. In those instances where a superficial study might suggest a difference—that is, in morbili and rubella—values for t and approximate values for P have been calculated which indicate that the difference is no more than would be expected by chance.

Although the overall incidence is so similar between the two groups, it might be that the age of incidence was different. Table III shows the average age of incidence in

TABLE III.—Average Age, in Months, of Contraction of the Zymotic Fevers

	"Milkless"	Breast-fed	t	P
Morbili	32.6	32.7	—	—
Rubella	27.3	32.3	1	0.3
Varicella	34.2	29	1.6	0.1
Pertussis	25	25	—	—
Epidemic parotitis	34	35	—	—

the two groups expressed in months, and again the parallelism is very striking. In the instances of rubella and varicella, the values of t and approximate values of P indi-

cate that there is no significant difference between the age incidence in the two groups for these diseases.

Consideration of these figures prompts the conclusion that breast-feeding makes no difference to the liability to contract zymotic fevers or to the age of incidence. These clinical observations lend colour, therefore, to the view that no immunity to the zymotic fevers is conferred on the human infant by the ingestion of colostrum or maternal milk and is in accord with previous anatomical, biochemical, and clinical observations on the transmission of antibodies to pyogenic infection.

In describing the results of a statistical investigation of this nature it is necessary to examine critically any possible sources of error. In fact, the 534 children in each group have been matched carefully enough that very few contaminants of significance have been allowed to obtrude. There is one, however, that deserves mention. Owing to the stringency necessary to ensure that none of the "milkless" group have received so much as a drop of colostrum or human milk, this panel has been recruited to some extent from illegitimate babies who have been adopted. Therefore the "milkless" group contains a larger number of this category than the breast-fed group. In view, however, of the secrecy which is maintained in many cases of adoption and which it is obviously desirable to preserve, it is not known how different the two groups are in this respect.

The effect of this contaminant might be considered in two ways. It might be alleged that illegitimate babies who were adopted were denied the care which they would naturally receive from their own mothers and so be more liable to contract infection; or it might be argued that adoption, with all its safeguards, placed the baby in the care of an unusually responsible person and so rendered it less likely to contract infection. If the former view were correct, a study of the figures reveals that in the instances of bronchitis and epidemic parotitis illegitimacy would act as a "positive contaminant" (making the results appear more different than they really are) and in the instances of morbilli and rubella it would act as a "negative contaminant" (making the results appear more similar than they really are). If the latter view were correct, these effects would be reversed. On all counts, therefore, this source of error may be regarded as a neutral contaminant and the most reasonable view to take is that it does not affect the issue.

Transmission of Antibodies

The problem of the transmission of antibodies from mother to offspring has been studied under three broad headings: the anatomical, the biochemical, and the clinical.

Work of a fundamental nature on the structure of the placental barrier was published by Grosser (1927), and his views as modified by Mossman (1926) are depicted diagrammatically in the accompanying figure. It will be seen that there are basically six layers which separate the maternal from the foetal blood and that this primitive arrangement is retained in pigs and horses, whose placentae are known, on that account, as epithelio-chorial. In the ungulates, such as cattle, sheep, and goats, the maternal epithelium has disappeared and these animals possess syndesmo-chorial placentae. In the carnivores a further simplification of the placental barrier has occurred and only the endothelium of the maternal layers remains, a placenta which is known as endothelio-chorial. In man, apes, bats, rodents, and insectivores all the maternal elements have disappeared and the maternal blood bathes the foetal placental tissues directly (placenta haemo-chorialis), whilst in certain of the rodents—namely, rabbits, guinea-pigs, rats, and mice—foetal capillaries project into the uterine lumina so that only a single layer of endothelium separates the maternal from the foetal circulation (placenta haemo-endothelialis).

It is known that antibodies are gamma-globulins of a molecular weight of approximately 160,000, and it is reasonable to suppose that these, together with albumins

(molecular weight about 70,000), might be able to negotiate the thinner types of placental barrier. It is known that all types of placental barrier are impervious to alpha-globulins (molecular weight about 1 million) and beta-globulins which contain large lipo-protein complexes.

Work of importance has been done on this problem by Moore, du Pan and Buxton (1949), who show that the gamma-globulins increase in humans in the blood during foetal life and decrease greatly during the first few months

The placental barrier in different kinds of animals (after Grosser). In all types of placenta the barrier is partially penetrated by both maternal and foetal capillaries. In the rabbit, antibodies are transmitted through the yolk sac rather than through the allantoic placenta.

after birth, whereas all the other protein components of the serum increase; furthermore, they showed that the ingestion of colostrum did not increase the antibody titre. On the other hand, in calves, foals, and lambs, gamma-globulins are absent at birth but rise steadily with the ingestion of colostrum.

Murray, Calman, and Lepine (1950), working with human subjects, have shown that both staphylococcal antitoxins (antihaemolysins) and antistreptolysins (Murray and Calman, 1953) are transmitted through the placental barrier and are found in higher concentration in the cord blood than in the maternal blood. Cashman (1955) has shown in the human that antibodies to pertussis, which are present at birth, disappear later, although the baby is breast-fed. Debré, Ramon, and Thierloix (1930) have demonstrated

TABLE IV.—Acquisition of Immunity

Type	In Utero	Via Colostrum
Man	+	—
Rat and mouse	+	—
Other rodents	+	—
Ungulates	—	+

tetanus antitoxins in the cord blood of immunized mothers, whereas colostrum contained no antitoxins, and Barr, Glenn, and Randall (1949) have demonstrated a higher concentration of diphtheria antitoxins in cord blood than in maternal blood.

Correlating the anatomical findings of Grosser with their own and others' biochemical investigations, Calman and Murray (1951) believe that the thickness of the placental barrier undoubtedly plays a part in determining whether immune bodies will pass to the foetus or whether the foetus must await their ingestion in the colostrum. Nevertheless, the relation is not an exact one and cannot be a matter of simple leakage or diffusion, as this would fail to account

for the *higher* concentration of antibody found in the cord blood in certain instances. Furthermore, in all categories of placenta there is considerable invasion of both maternal and foetal elements by maternal and foetal capillaries respectively, thus reducing the apparent barrier; and in the rabbit it is the yolk sac placenta and not the allantoic placenta which is responsible for the transmission of antibodies (Brambell, Hemmings, and Rowlands, 1948). Probably a specific fraction of the antibody penetrates the placental barrier and the complete globulin is resynthesized on the foetal side. Murray and Calman picture the mechanism of antibody reception in different kinds of animal as set out in Table IV.

If these views are correct, therefore, we should expect that in the human breast-feeding would confer no specific protection against those diseases leading to antibody formation.

Discussion

Various studies have been made from time to time comparing the health history of babies who have been breast-fed with those who have been bottle-fed. Stevenson (1947) and Norval and Kennedy (1949) found little difference in the sickness rate between the two groups. An important study was undertaken by Stewart and Westropp (1953) on babies born in the Oxford district. The 580 babies recorded were divided into four groups. Those in group 1 were weaned in the first month; those in group 2 were weaned in the second or third month; those in group 3 in the fourth or fifth month, and those in group 4 after five months. These workers found that the bottle-fed babies were somewhat heavier than the breast-fed ones, but that the milestones such as sitting up, walking, and the appearance of teeth were not very different in the four groups. The incidence of gastro-enteritis, bronchitis (or bronchopneumonia), and otitis media were specifically contrasted in the four groups, and, again, little difference could be detected.

The present series differs from the Oxford series in that one group has not received so much as a drop of human milk and the other group has received some human milk, although the duration of lactation is unknown. The comparison, therefore, is a direct one between "no milk" and "milk," and thus answers slightly different questions from those posed by the Oxford investigation. The present series suffers in comparison with the Oxford series, however, in that the babies and children were not examined personally but the diagnosis of the parent (if clear cut) or of the family doctor (if the parent's diagnosis was obscure) has been accepted.

Another important by-product of this investigation is concerned with the incidence of multiple sclerosis in the two groups. Platt (1955) has pointed out how it is not known whether galactose can be synthesized by any tissue other than the breast, and thus, if an infant is fed on cow's milk rather than human milk, it may receive much less than its proper quota of galactose. Further, it has been shown (Stearns, 1939) that infants fed on cow's milk store nitrogen at a higher rate than those fed on human milk. Platt argues that this nitrogen is laid down in muscle and that the rapid development of muscle tissue in these artificially fed babies would be paralleled by a rapid rate of myelination of the nerves. Now it is in just these children that the galactose required to elaborate galactocerebrosides for myelination purposes is deficient, and Platt suggests that myelination may take place by means of glycerocerebrosides. This unnatural myelination would persist throughout life and perhaps render the nerves more susceptible to whatever is the immediate insult responsible for multiple sclerosis.

Lumsden (1951) has propounded the view that this is a myelinolytic enzyme, cerebrosidase, which may readily hydrolyse the glycerocerebrosides and to which normal glucocerebrosides are more resistant. A study, therefore, of the incidence of multiple sclerosis in a population of artificially fed babies as compared with a population of

breast-fed babies might be rewarding, particularly as multiple sclerosis is a rare disease amongst those races in whom lactation is prolonged for two or three years. It must be pointed out, however, that the incidence of multiple sclerosis amongst the general population is in the region of 35 to 65 per 100,000 (Limburg, 1950) so that a very much higher incidence amongst the artificially fed babies and also a panel of many thousands would be necessary to reveal such a tendency. Finally, R. S. Allison (1957, personal communication) reports a case of multiple sclerosis in a patient who had been nursed at the breast as an infant for three years.

Summary and Conclusions

The reasons for establishing a series of parallel groups of children, the one fed on human milk and the other which has never received human milk, are discussed in relation to the possible aetiologies of carcinoma of the breast.

A study of two groups of children, each numbering 534, one of which has received human and the other which has never received human milk, fails to reveal any difference in the total incidence or age of onset between the two groups in relation to the zymotic fevers and certain pyogenic infections.

These observations support the view that antibodies to the zymotic fevers, like antibodies to pyogenic infections, are not transmitted in the human via the colostrum or in the maternal milk.

The anatomical and biochemical evidence is described supporting the view that, in the human, antibodies are transmitted from mother to offspring *in utero*.

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