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47

WORKING GROUP

ON:

MENTAL DEFICIENCY

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EDITED BY

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SCIENTIFIC PAPERS

« Nel novembre scorso, durante la riunione di un Gruppo di lavoro, la Pontificia Accademia delle Science, nella sua costante opera a servizio dell'umanità mediante la ricerca scientifica, ha approfondito lo studio di una particolare categoria di handicappati, quelli mentali. La debilità mentale, che colpisce circa il tre per cento della popolazione mondiale, dev'essere presa in speciale considerazione, perché costituisce il più grave ostacolo alla realizzazione dell'uomo. Il rapporto del menzionato Gruppo di lavoro ha meso in rilievo la possibilità di cure preventive delle cause di debilità mentale, mediante opportune terapie. La scienza e la medicina offrono dunque un messaggio di speranza e insieme di impegno per tutta l'umanità. Se soltanto una minima parte del "budget" per la corsa agli armamenti fosse devoluto per questo obiettivo, si potrebbero conseguire importanti successi e alleviare la sorte di numerose persone sofferenti ».

(Dal Messaggio di Sua Santità Giovanni Paolo II per la Giornata della pace, Capodanno 1981)

INTRODUCTION

The Working Group organized by the Pontifical Academy of Sciences which took place from November 3rd to November 6th 1980, had as its purpose the study of a problem of the greatest significance to mankind. Mental illness afflicts, in a conservative estimate, three per cent of the world's population and as pronounced by His Holiness Pope John Paul II in his Peace Message delivered on January 1st 1981, "should receive special attention as it constitutes the greatest obstacle to the full realization of man".

By bringing together at the seat of the Academy a group of eminent specialists, my purpose was to highlight this momentous question, even if only a very small fraction of it could be approached. The problem is a very vast and complex one. It is appalling to learn that all the information we have points to the fact that due to biological, socio-cultural and economic causes, mental illness is increasing and will increase even more.

Together with the biological problems, where more information on genetics, chromosomal traits and intrauterine life is necessary, socio-economic factors are of the greatest significance. The scientific approach has undoubtedly gained bigger momentum in recent decades and great progress is expected and achieved every year through research undertaken in the fields of genetics and chromosomal cytochemistry, as well as with results obtained by those who study the biochemistry of the brain. This is a field where multidisciplinary approach has shown its importance. The fairly new interest on prenatal or foetal physiology brings to this approach the most significant contribution. The same may be said for the study of the newborn child, who has—for some specialists—at least during the first month of existence, a "proper brain biochemistry", which makes him different from the being who will outgrow him. Scientific research is thus advancing in this field, albeit slower than would be desired.

In the field of learning mechanisms, progress has also been achieved, again in an understandably slow pace. One of the papers included in this book shows how important may be the precocious use of sensorial stimuli for the improvement of cognitive mechanisms.

In the field of socio-economical and cultural variables affecting mental deficiency, much has been said, but it has only been possible to express the data in a quantitative way. However, there can be no doubt about the positive influence of wealth, nutrition and intellectual environment on the mental development of children. Their performance in school, as well as their social behavior as a whole, is a clear-cut proof of these factors. Poverty, as found in developing countries, is not only a co-factor but a factor per se *of mental deficiency. Notwithstanding the fact, rare but not negligible, an abusive type of education may, even in affluent homes, lead to deficiencies. Thus, in developing countries, and in the inhuman dwellings found in so many cities of the industrialized countries, the greatest attention must be given to nutrition of pregnant women and of the newborn child on acconut of its importance. However, one must not forget how much better integrated, in family and society, are the mentally deficients who live in the poor human agglomerations, particularly in developing countries, than in the affluent societies of the same countries. The tendency is to abscond or isolate them in hospitals. The mentally deficient, child or adult, needs attention, understanding, tenderness and comprehension, as much as mental and pharmacotherapy.*

We concluded from our discussions, held during the vivid days of our meeting, that more knowledge must be obtained through research and that practical application of already existing knowledge of methods of prevention and diagnosis should be extended. Why, for instance, in some countries is early diagnosis of phenylketonuria restricted to the privileged classes, and futhermore, why in other countries is this method of prevention not used at all? It also became clear that in order to prevent mental deficiency, more knowledge should be gained and that precise early diagnosis can increase the efficiency of therapy.

Together with prevention, great attention was given during the meeting to aid. The problem of a mentally deficient human being pertains not only to his family but to society as a whole. Wards, schools, homes, special education for the deficients, as well as care and assistance for the families of these handicapped individuals, are a responsibility which the State cannot overlook. Like a normal being, a mentally deficient person has his rights which society has the duty to preserve and enhance.

Let me end this introduction with a word of optimism. It comes on one side from the devotion of those who have dedicated their life to lessening the suffering of mental deficients and tells us how much their lives have been enriched by their experience; on the other side, from the firm belief that science will overcome in the near future at least a great part of this human scourge.

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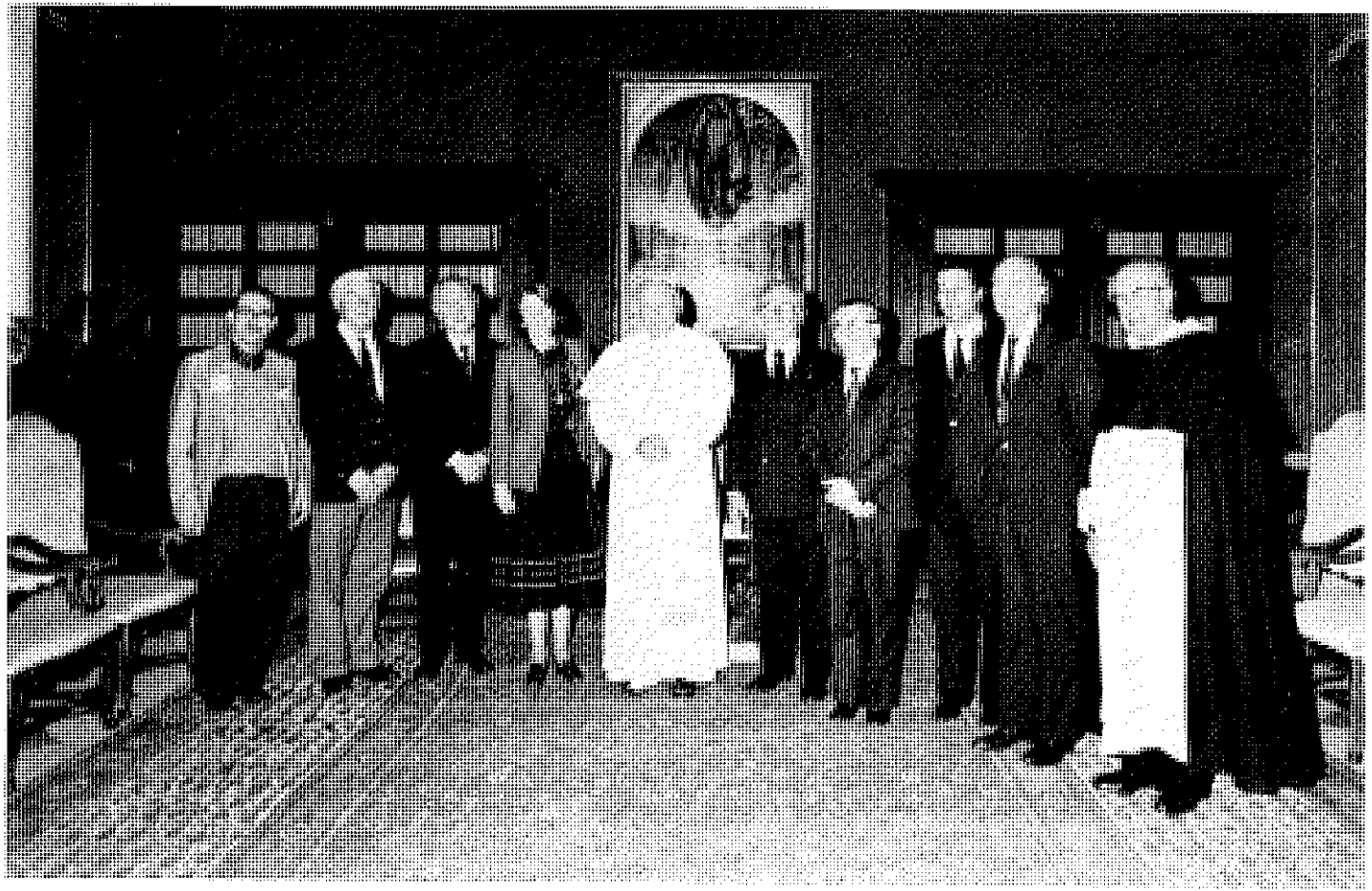

SCIENTIFIC PAPERS

THE DEFICIENCY OF THE INTELLIGENCE

J. LEJEUNE

The most specific of human illnesses, because only man can suffer from it, is also the most inhuman, because it deprives the sick person of the most precious part of our natural heritage.

Indeed mental illness is only a symptom because an enormous number of diseases, from traumas, infections and intoxications to genic and chromosomal illnesses, can cause it. But a simple example can help us put a little order in this jumble of human catastrophes.

THE SUBSTRATUM OF THE INTELLIGENCE

When Pascal discovered that one could imitate arithmetical calculation by a combination of cogged wheels and graphs, he proved at the same time that it was possible to introduce logic into matter if it is duly shaped.

The computers of today are much more refined and use many of the properties of matter and of energy (deflection of jets, migration of magnetic bubbles, laser impulses or semi-conductors of printed circuits), but all these machines, like Pascal's, meet three fundamental requirements:

1. A pre-established chart, logically constructed
2. Transmission across distance that is clear and without dispersion
3. An honest response of each component, without hesitation and without delay.

To think that machines are a model of thought would be to think mechanically, hut to recognize that they can comply with the requirements of reason can help us to grasp some important analogies.

All mental illnesses are in effect characterized by one or several breakdowns, violating one or more of these three requirements.

THE NETWORK OF THE MIND

Our brain surpasses (and for the present by far) the most important machines. Some eleven billion neurons, interconnected by some eleven million millions of synapses, that is an astronomical figure. The length of the cable system which unites this ensemble is equally astronomical. If we separated the nervous fibres which are visible to the optic microscope and placed them end to end, they would reach from here to Tokyo. But if we take into account the bundles of neurotubules, which would possibly be the basic cable network, it would go from here to the moon and back again!

Despite the brilliant discoveries of neurology, the detailed plan is largely unknown to us. Yet, just as a repair man who sees that one of the drawers of a computer is broken can locate the trouble of the machine, so the most serious anatomical damage can reveal certain diseases.

If a part of the network is lacking, such as the arrhinencephaly of the trisomie 13, the over-all machinery is seriously damaged. Likewise, secondary damage from hemorrhage, from ischemia, from infection or tumoral compression, or even from progressive lamination of the brain under the hydraulic pressure of hydrocephaly, can cause the deterioration of this precious network.

Every attempt at repair seems in vain, for the neurons cannot be replaced, but prevention can be effective, as is shown by the derivation of cephalorachidian liquid to compensate hydrocephaly.

In certain cases the disease itself can be prevented.

In the Anglo-Saxon countries the abnormalities of the neural tube, from spina-bifida to complete anencephaly, are one of the most serious causes of cerebral deficiencies.

Until very recently it was known only that defects in the neural tube—as the ensemble of these malformations is called—present a strange geographical and sociological distribution. While they are rare or almost unknown among Mediterranean people, their frequency increases as we go northward. In the British Isles one child out of every 500 is affected.

On the other hand, it was known that mothers who had already had a child with this defect ran a much higher risk (about 5 percent) of having another child with the same defect. Finally, children of poor mothers seemed to be more frequently affected than those of rich mothers, and Renwick (1) noted a strange correlation between the frequency of the disease and the consumption of products of poor quality (blighted potatoes for example). All this constituted a difficult picture to understand. How-

ever, since the opening in the neural tube permits the flow of α-fetoprotein, the amount of this substance increases in the amniotic fluid and even in the mother's blood. Hence a possibility of detection in the mother and then of confirmation by analysis of the amniotic liquid.

There was even set up in England three or four years ago a huge and costly program for systematic detection with a view to eliminating the sick fetus by induced abortion.

Again, a recent discovery of Smithells (2) shows that the correct procedure for medicine is never to attack the patients but rather the disease. Basing himself on available information—sociological, geographical and alimentary—and bearing in mind the findings of Hibbard and Hibbard (3), which showed that mothers of children so affected had a low blood folate rate, Smithells treated the expectant mothers (who had already had a child with this defect) with a multivitamin preparation administered before conception. Out of 178 infants, only one was born diseased instead of the 8 or 9 expected. In a test group of mothers not so treated, he observed 13 sick babies out of 260, exactly as the statistics predicted.

Besides the relative deficiency of fresh fruits and vegetables in northern countries, two other conditions explain the high frequency in the British Isles: prolonged boiling as well as conserving destroy the folates. Likewise, the use of oral contraceptives tends to diminish the rate of blood folate.

These facts corroborate the atrocious statistics of Tiersch (18), who by administering aminopterine (antifolic) to a group of 24 mothers from 3 to 8 weeks pregnant produced "experimentally" in the majority of the fetuses serious malformations of the central nervous system (anencephaly, spina bifida).

It is of course too early to draw the conclusion that anencephaly and the problems of the closing of the neural tube will be definitely avoided by a preventive vitamin therapy, just as smallpox is avoided by vaccination; but for the first time this formidable and mysterious disease now seems to be on the way to being conquered.

Transmission and insulating substances

A second requirement is that it is important that the network permit transmittal without loss and avoid any parasitic diffusion. We all know that the most refined set-up can be destroyed by a short circuit, by solderings which shrink, or by wandering currents.

Genetic pathology provides us with a large number of examples of "diseases of the insulators". We know little about the real short circuits between bare fibres which intertwine, but we do know certainly that the successive stages of the myelinization of a child's brain correspond in every detail to the acquisition of motor or mental functions corresponding to the portion of the brain involved. The order in which the areas become myelinized is the same as that of neurological acquisitions.

On the other hand, we know of many diseases in which the building up or the tearing down of the molecular constructions which constitute the insulators is deficient. The intermediary products then accumulate in the neurons and kill them. Suffice it to mention the Nieman Pick disease (Sphyngomyeline), the Gaucher disease (Glucosyl-ceramide), the Krable disease (Glalactosyl-ceramide), metachromatic leucodystrophia (Sulfatides) and the Tay Sachs disease and Sand'hoff's disease (Gangliosides).

These "diseases of the insulating bodies" explain only a tiny part of the long chapter regarding the delays in myelinization and the global deficiencies in the growth of the brain (microcephaly), which are probably much more important numerically but of which the precise causes are yet to be discovered.

The response of the components

The binary logic used by machines summarizes very simply the elementary principle of logic, namely, that A cannot be non-A—in other words the impossibility of being something and at the same time not being that something. In good logic every step is described in one word: yes or no. All that is uncertain must be eliminated, which is moreover understandable since reason is only a means of eliminating the fortuitous in order to retain only what can be inferred or arrived at by deduction. The doors used by information workers to simulate logical concatenations strongly resemble those of Musset: "Il faut qu'une porte soit ouverte ou fermée" (a door must be open or closed). If the door is left ajar, or the tooth of a gear slips, the argument does not hold up.

But the "doors" of neurons are infinitely more complex than those of electronics. At each synapse the exciter cell releases into the intersynaptic space a particular molecule, a chemical mediator (acetylcholine, noradrenaline, serotonine, etc.). The chemical mediator then activates

the membrane of the next cell, forcing it to open its "ionic pores", which are really ionic traps that so far have defied all attempts to describe them precisely (4). The appropriate mediator is recognized by its reactive surface, a little bit like the security key adapts to the appropriate lock and only that lock.

This specific adaptation makes it possible to identify in the complicated maze of the networks, functional systems which probably correspond to the principal cerebral functions, and each uses its own personal molecular language (whether it be the motor system, the pain transmittal system, the system that governs mood, etc.). It is this specificity which makes it possible to understand the pharmacological action of certain drugs affecting almost exclusively this or that system.

Without going into the detail of the reactions, we can assume that the molecular machinery must be one of extreme precision in order to produce at the proper moment, in the proper amount and at the appropriate site, this or that mediator molecule, and to assure its subsequent inactivation or recuperation.

It is possible that many mental diseases in which one can see neither great anatomic destruction nor apparent lesion of the insulating sheaths are the product, in the final analysis, of a difficulty in the supply of proper mediators.

An extremely simplified picture of these chemical years makes it possible to understand this better.

By putting into this pseudo-Pascalian machine the enzymatic blockings corresponding to genetic diseases which we know produce a weakness of the intelligence, we note that certain points are grouped in clusters. On the one side the diseases of the insulators (cf. above) and on the other the abnormalities of the mucopolysaccharides (indispensable for the production of the membranes).

There remain all the other points which at first sight seem distributed in no particular order. What relationship can there be, for example, between phenylketonuria (absence of hydroxylation in -4- of the phenylalamine in tyrosine) and homocystinuria? A detailed analysis, point by point (5), shows that these blockages have at least one effect in common: they decrease the supply of monocarbon radicals entering the cycle of the folates. Here we find again that vitamin which we mentioned at the beginning in connection with the defects of the closing of the neural tube. And this is indeed not by chance. It might very well be that the metabolism of the monocarbons is of primary importance for the functioning and for the construction of the entire cerebral structure.

Hypothesis of the monocarbons

At first the production of the components of myeline requires the methylation of phospholipids. And thus an intense activity of the monocarbon cycle, of which the folate is the carrier, in the course of the setting up of the nervous system. Moreover, the production of chemical mediators, such as acetylcholine in particular, requires the same activity. Finally, the activation of certain mediators (adrenaline), or their inactivation, also requires appropriate methylations.

We see that monocarbons are the smallest stone to lay in building the cerebral structure, but also the most frequently used in the most diverse places.

Therefore the general hypothesis, at present purely heuristic (5), that the problems of replenishment of raw materials (precursors of monocarbons), or the problem of the transport of monocarbons (cycle of the folates) or of their actual utilization (transmethylases) could be of crucial importance. A double argument supports this point of view. First of all, the brain possesses a sort of folate pump, such that the cerebral concentration is always very superior (four times more) to the concentration in the rest of the organism; and even in the case of lack of folate the amount in the blood or in the liver drops long before the cerebral reserve is affected (7).

Moreover, all the diseases which block the transformation of the folates, or the transport of monocarbons towards the transmethylases (with the serious lack of B-12) all produce serious neurological syndromes (7).

But the diseases due to chromosomal abnormalities are difficult to place in this general framework. In fact, the excess or deficiency of chromosome segments or of entire chromosomes cause, depending on the chromosome involved, a particular syndrome which can be clinically identified. Even if one compares the excess of chromosome (trisomy) and the deficiency of the same element (monosomy), the two resulting syndromes are like in a mirror, countertypes (8): the excess accentuates this or that morphologic characteristic in one direction, and the lack accentuates it in the opposite direction.

But when the intelligence is involved, this difference is not found; for example, if a chromosome 21 is in excess (trisomy 21) or if it is partially lacking (monosomy 21 in mosaic), the result is always the same: a serious mental deficiency.

Moreover, each time that there is a deficiency or an excess of an

important segment of no matter what chromosome, there is always a more or less dramatic effect on the intellective functions. Without trying to summarize here all the chromosomal pathology, we will mention only the most frequent syndrome: that of the trisomy 21.

Particular case of trisomy 21

We know for example that the synthesis of several enzymes is controlled by the genes located on chromosome 21.

The SOD-1 in area q 221 is 1.5 times more active in the trisomy 21 (1) (10), which corresponds to the fact that these possess three genes instead of the normal two, thus producing three quantities of the corresponding enzyme (instead of the normal two).

Likewise for the Glycinamide ribonucleotide synthetase (11) (12) (13).

In the present fragmentary state of our knowledge (only one other gene of the 21 is known: the one which controls the production of a protein which is sensitive to interferon), it would be premature to try to explain all that we know of the trisomy 21 on the basis of these three reactions, which are accelerated in these patients.

Yet an analisis of comparative pathology, that is of the diseases of which certain major symptoms resemble some of those found in trisomy 21 (hypothyroidism, iminodipeptiduria, Alzheimer's disease, Lesh Nyhan's disease, etc.), or on the contrary are the opposite of these symptoms (homocystinuria), makes it possible to show (5) that the probability of a deficiency of monocarbons is very great in trisomy 21.

If this is really true, then analytical therapeutic trials could be planned.

One direction for research

Although the information available at present is still too fragmentary, a possibility for experimental research regarding the role of monocarbons seems to be offered us by another chromosomal disease, very different *a priori,* the Xqfra 27 or 28 syndrome.

In certain mental defectives, usually boys, one notes a fragile area in the distal part (27) of the long arm of the chromosome X (hence the name Xqfra). A culture medium low in folate very frequently produces a lack on the chromosome X of the cells in vitro. On the contrary, if the medium is rich in folate or formyltetrahydrofolate, tbe fragile area is not apparent. This discovery (14) (15) was recently con-

firmed and completed (16). When we add systematically to the culture medium low in folate, substances which can supply monocarbons radical (serine, hydroxyproline or 5-amino-levulinate for example), we see that also these "precursors of monocarbons" are capable of preventing the manifestation of the chromosomal fragility.

It is of course too early to say that these *in vitro* results can be applied *in vivo,* that is, to carry on an effective therapy of the patients. Although we already have some slightly favorable clinical indications, it is too soon also to attack the crucial question: the correction of the metabolic difficulty; supposing that it is entirely possible, would this produce an improvement in mental development?

Yet it seems plausible that this chromosomal detail can provide us with a very valuable experimental tool: one would simply have to take a few drops of blood and then carry out these tests in the laboratory. For the first time a disease which is at the same time chemical and chromosomal and directly related to a mental deficiency can he analyzed *in vitro.*

Conclusion

Concluding this too brief and too general review, certain broad lines of research in the prevention and treatment of mental diseases can already be outlined.

The role of the metabolism of monocarbons, heretofore limited to the synthesis of nucleic acids and therefore to hematologic or neoplasic diseases, seems to go far beyond the limits of this classical, narrow frame. Already the acquired pathology reveals important neuropsychological correlations between the use of folates and the cerebral functioning (17), thus leading very clearly to the hypothesis herein presented.

It would be unreasonable to think that all mental pathology, including congenital deficiency of the intelligence, can be related to one metabolism alone, but it seems clear that the field of research is wide open. Especially, from the patient detection of the genes carried by the chromosomes responsible for the major trisomies and monosomies, to the understanding of their metabolic effects through comparative analysis of the many genic diseases already known, a concentrated attack now seems possible.

The difficulties of such an endeavour are great, and the path length of the road to be covered is unpredictable—all the more reason to persevere.

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CONTRIBUTIONS TO THE MOLECULAR BASIS OF MENTAL RETARDATION

F. MAYOR

The molecular pathology of brain disfunction in some inherited and acquired metabolic diseases during the neonatal period has been established. It is noteworthy that the interference with the myelinization process might be the convergence point that could explain the pathogenesis of mental retardation in several of these diseases at the molecular level.

At the present, we are investigating the effects of the local hyperbilirubinemia on the hrain function during development. On the other hand, it is interesting to establish the relationship between tubuline alterations and the Down's syndrome, mainly in tbe aged mothers.

In each section of this review the principal investigator and collaborators are mentioned, and the relative references of each subject are included.

The references of review articles comprehensive of the molecular basis of the mental retardation, are also included.

I

PERINATAL BIOCHEMISTRY: THE PREMATURE NEWBORN

J. M. MEDINA, C. ARIZMENDI, M. BENITO, J. M. CUEZVA, F. MORENO

The aim of this research is to study the biochemical behaviour of the premature newborn. The study of the metabolism of the premature newborn may contribute to the molecular basis of the clinical risk undergone by the premature neonate in the adaptation to extrauterine life. In addition, this study may contribute to the understanding of the changes in the fetal metabolic machinery as a theleonomic or casual consequence of the ontogenic development.

In order to board this problem we have studied tbe metabolism of the mature and premature newborn rats during the presuckling period. Since during this period the onset of suckling has not occurred, the newborn has to use its own energy reserves, which makes it possible to test the fitness of neonatal metabolism without interference of the exogenous substrates from mother's milk.

The major metabolic fuels utilized by the neonate during the presuckling period were glucose from liver glycogen, lactate and alanine (1). Premature neonates also used glucose, lactate and alanine but prematurely delivered newborns showed a transient resistance to lactate utilization which was enhanced by hypothermia (2). *This resistance to lactate utilization is a shortcoming for the premature newborn not only because of the delay in the utilization of a relevant metabolic fuel but also because of the persistence of lactiacidaemia and subsequent acidosis.* Therefore, we have investigated the fate of lactate in these circumstances (3). Unexpectedly, our results have shown that gluconeogenesis from lactate is insignificant during the presuckling period (1, 3). Instead our findings support the idea that lactate is consumed immediately after delivery as a consequence of its oxidation through the tricarboxylic acid cycle (3). In addition, this suggestion would also account for the observation that lactate utilization depends on oxygen supply (4). Thus, the increase of oxygen supply enhanced the rate of lactate utilization together with overcoming the resistance to lactate utilization shown by premature newborns. These results pointed out that oxidative metabolism plays an important role in the energy supply during the early neonatal period. Moreover, the effect of the increase of the oxygen supply on overcoming the resistance to lactate utilization shown by premature neonates suggests that premature tissues undergo hypoxia during the early neonatal period. Actually, we have observed that the metabolic behaviour of the experimentally hypoxic mature neonate is very similar to that shown by premature neonates (5). Our research in progress is devoted to dilucidate whether the bypoxic metabolic behaviour of the premature newborn is due to decreased oxygen availability or to the immaturity of the mitochondrial machinery (6) which prevents proper utilization of the available oxygen.

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II

MOLECULAR PATHOLOGY OF BRAIN DISFUNCTION IN INHERITED METABOLIC DISEASE

A. PHENYLKETONURIA

F. VALDIVIESO, J. BENAVIDES, C. GIMÉNEZ

Phenylketonuria is an inborn error of metabolism produced as consequence of the genetically-linked deficiency in the hepatic phenylalanine hydroxylating system. In "classical phenylketonuria" the deficiency in the activity of phenylalanine 4-hydroxylase enzyme leads to a considerable accumulation of phenylalanine and consequently to an increase in the concentration of its metabolic products in the tissues and fluids of patients with uncontrolled disease. Treatment with a phenylalanine restricted diet lowers phenylalanine levels and prevents clinical symptoms of the "classical" disease. The clinical features of untreated phenylketonuria include severe mental retardation, microcephaly, pigment dilution and a variety of neurological and behavioural symptoms such as seizures, hyperactivity, agitated and agressive hehaviour and electroencephalographic abnormalities.

In spite of the number of studies on the pathogenesis of phenylketonuria, the biochemical mechanisms by which increased phenylalanine and/or its metabolites cause brain disfunction are still subject to research. There is almost general agreement that a phenylketonuric patient is mentally normal at birth and that a progressive loss of intelligence occurs during his first years of life, precisely when the myelinization process is also occurring. It is noteworthy in this respect, that impaired myelinization has been observed in the brains of patients with untreated phenylketonuria. Since protein -cholesterol- phospholipid complexes appear to be precursors of myelin, impairment of myelin synthesis may result from interference with the synthesis processes of any of its components.

To determine how phenylalanine exerts its effect studies were devel-

oped in rats with experimentally induced phenylketonuria-like characteristics (1, 2). Since the transport of any particular amino acid into the brain depends not only on its own concentration but also on the concentrations of the other amino acids in the blood, raised levels of blood phenylalanine cause the exclusion of amino acids from the brain because of the inhibition of their transport mechanisms (3). The alteration of the free amino acid pool in the brain results in the reduction of the protein synthesis rate since this process depends on the free amino acid concentration in the brain.

The study of the *in vivo* effects of high circulating phenylalanine on the glycolytic pathway in the brain of rats with experimental phenylketonuria showed that phenylalanine interferes with glycolysis leading to a decrease of pyruvate concentrations (4).

Until recently glucose was supposed to be the only substrate for brain metabolism. However, it is well established now that ketone bodies in developing brain are utilized both for respiration and providing the acetyl-CoA required for the synthesis of the lipids involved in the myelinization process. Studies on the effects of phenylalanine and its metabolites on the enzyme activities of ketone body utilization in the brain of suckling rats indicated that the process is markedly inhibited (5). *This inhibition of the ketone body utilization in brain leads to a decrease in the availability of Acetyl-CoA for respiration inside the mitochondria, as well as for the supply of carbon skeleton for synthesis of cholesterol and fatty acids in cystosol.* Since rates of myelinization and ketone-body utilization parallel during brain development, if there is a relationship between both processes, any inhibition of the ketone body utilization during the early stages of brain development might have detrimental effects on myelinization.

All these biochemical features—impairment of ketone body utilization, inhibition of glycolysis and depletion of free amino acid pool in the brain—could therefore explain the pathogenesis of the mental retardation that is characteristic of phenylketonuria on the basis of a mechanism involving defective myelinization during brain development which might be expected to lead to permanent defects in the nervous system.

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B. HYPERGLYCINEMIA

M. UGARTE, J. BENAVIDES, M. L. GARCÌA, J. LÓPEZ LAHOYA, F. MAYOR, JR., F. VALDIVIESO

Glycine synthase activity in the rat brain has been shown to be high during the postnatal period. The function of this enzymatic system together with serine hydroxymethyltransferase *represents the major mechanism for the generation of one-carbon pool* (1). This could account, at least in part, for the myelinogenesis anomalies seen in patients with glycine encephalopathy (deficiency in brain glycine synthase or non-ketotic hyperglycinemia).

Glycine must penetrate the mitochondria to be metabolized. We have demontrated that glycine is taken up by the liver and brain mitochondria by a carrier-mediated process without requiring energy. The glycine uptake by brain mitochondria is not Na^+ gradient-dependent either (2).

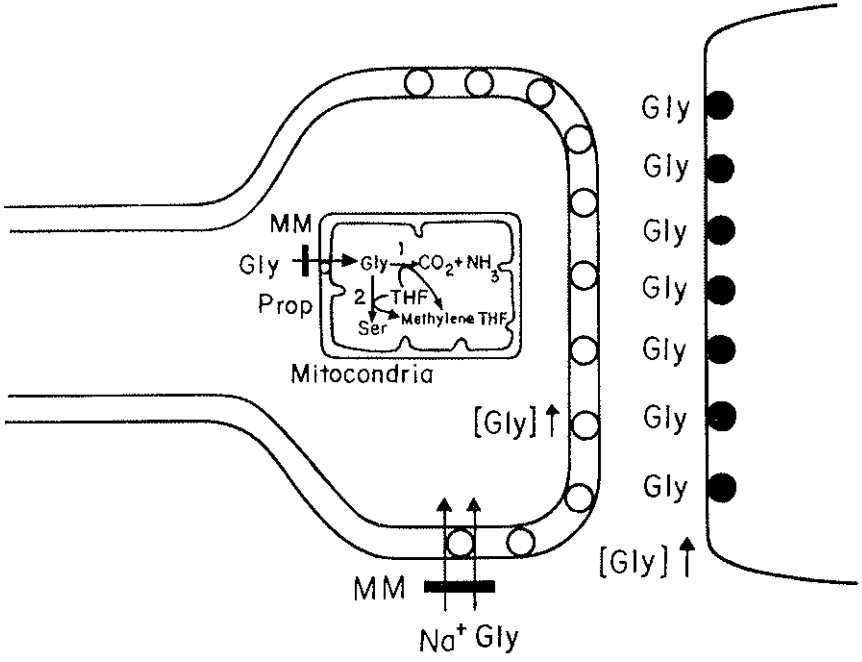
The etiology of hyperglycinemia in propionic acidemia and methylmalonic acidemia disease (also known as ketotic hyperglycinemia) were demonstrated. Propionate and methylmalonate inhibit the transport of glycine across the mitochondrial membrane at physiopathological concentrations (approximately 95% inhibition at 5 mM propionate and/or methylmalonate) (3).

Glycine has been reported as an inhibitory neurotransmitter in the C.N.S. mainly at the spinal cord level. We have studied the properties of the glycine transport system in brain synaptosomal membrane vesicles (4). We also have tested the effect of methylmalonate and other metabolites accumulated in organic acidemias. Among these compounds tested at 2 mM concentration, only methylmalonate significantly inhibited the glycine sinaptosomal uptake (5). Since glycine uptake is the mechanism for the termination of the action of the released transmitter, the inhibition of this uptake could produce an increase of the glycine levels at the

synaptic cleft *that would interfere with the normal function of the inhibitory neurons in the spinal cord.*

The postnatal development of glycine synaptic receptors has been studied. We have found that in the rat glycine receptors, as measured by the strychnine bindings, appear postnatally. In rats with experimental hyperglycinemia, strychnine binding to spinal cord glycine receptors increases much more rapidly reaching a level of 1.5 times the the control value by day 10 (6). In conclusion we believe that the increased number of glycine receptors in hyperglycinemic rats should be responsible for the neurological damage in non-ketotic hyperglycinemia. This is not, however, ignoring the possible deleterious effect of a shortage of methylene tetrahydrofolate due to the lack of glycine synthase activity.

We summarize in the diagram the brain glycine metabolism, mitochondrial and synaptosomal uptake and biogenesis of receptors which we have found in hyperglycinemia (ketotic and non-ketotic).



1 – Glycine synthase
2 – Serine hydroxymethyltransferase
○ – Glycine reuptake system
● – Glycine receptor
MM – Methylmalonate
Prop. – Propionate

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C. HYPOTHYROIDISM

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The knowledge of the molecular basis for the developmental retardation that commonly accompanies congenital hypothyroidism is incomplete. The relationship between congenital hypothyroidism and brain disfunction is still unknown.

Studies of the brains of hypothyroid patients and experimental animals made hypothyroid have shown a reduction in myelin lipids and a non-selective reversible delay in myelinization.

We have examined the effects of hypothyroidism on the activity of several key enzymes (1-3) involved in biosynthetic processes in the brain during development. Rats are made hypothyroid by administering n-propylthiouracil in the drinking water given to the mother from the 12th day of gestation and throughout the suckling period. Serum triiodothyronine and thyroixine levels are low in hypothyroid status.

The diminished activities of pyruvate kinase (1), 3-oxo acid CoA-transferase (2) and malic enzyme (3) in the brain of hypothyroid animals are consistent with the idea that thyroid hormones promote the biochemical development of the brain and suggest that *in hypothyroidism an impairment of lipogenesis would lead to delayed myelinization and hence to brain disfunction.*

Since the maximum rate of myelinization occurs during the early

stages of brain development, the effect on lipogenesis during this period might have detrimental effects on this process and might thus be responsible, at least in part, for mental retardation in congenital hypothyroidism.

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III

EARLY POSTNATAL DIAGNOSIS OF INBORN ERROR OF METABOLISM

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	Screening program	Pediatrics hosp.	Total
Number of analysis*	104.282	5.816	110.098
Amino Acids Metabolism			
Phenylketonuria			
classic	12	20	32
hyperphenylalaninemia	3	—	3
malig. hyperphenylalaninemia	—	1	1
Maple Syrup Urine Disease	—	8	8
Non-ketotic Hyperglycinemia	2	5	7
Tyrosinemia Type 1	2	1	3
Others	5	9	14
Organic Acids Metabolism			
Propionic Acidemia	2	5	7
Methylmalonic Acidemia	—	4	4
Others	1	—	1
Amino Acids Transport			
Cystinuria	3	7	10
Others	5	8	13
Carbohydrates Metabolism	2	2	4
Mucopolyssachariduria	4	10	14

* Until October 1980

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ACQUIRED MENTAL RETARDATION OF FETAL AND PERINATAL ORIGIN

A. W. LILEY

Aetiological classifications of mental retardation—typical is P. A. Harper's table for USA (Table 1)—reveal that specific identifiable causes account for only a minority although understandably a higher proportion of the severe retardation found in institutions. Of retardations with an identifiable cause, acquired handicaps of prenatal or perinatal origin account in turn for only a fraction. The size of this fraction depends on the age at which retardation is classified, being higher in early life for two reasons. First, at this time there has not been added the quantum of

TABLE 1. *Aetiology of mental retardation (USA)* (P.A. Harper, 1962)

	Percentage	
	Large institutions	All retarded
a) Familial or cultural	40	65-75
b) Genetic: mutant genes	5	1
chrom. abnormality	8	5
c) Acquired: prenatal	3	1
postnatal	10	2
d) Unknown	30	15-25

handicap acquired in childhood, adolescence and adult life—from encephalitides and meningitides, poisonings, trauma, degenerative diseases, etc. Second, only the more flagrant syndromes or signs are recognised in the neonate and young infant. Because in real life the mildly and moderately retarded outnumber the severely and profoundly retarded, the subsequent demands of communication, of schooling, of social conformity and of employment reveal a substantial number of handicapped

whose early progress was unremarkable and whose retardation was initially unsuspected.

Strictly, mental retardation is not diagnosed in the neonate at all but merely inferred or presumed from the recognition of risk conditions such as hydrocephaly or congenital rubella or from the presence of such signs as poor suckling or swallowing or muscular hyper- or hypotonia. As has been remarked, given three babies in adjacent bassinettes—one normal, one with classical trisomy 21 and one with hydranencephaly, there might well be little difference in their behaviour, their response to simple stimuli and the findings on superficial neurological examination to distinguish between them.

This fact, that retardation is presumed or inferred from the recognition of certain syndromes or signs itself carries a danger, that of labelling by which the prophecies become self fulfilling. The fastest way to make sure someone is ineducable is to decide they are ineducable. Therefore, even in conditions where mental retardation is of moderate or even high incidence, care must be taken that rejection and institutionalisation do not aggravate the retardation of those who are retarded and produce retardation in those who are not.

In this context it is important that both health professionals and lay people realise that for a large number of adverse fetal and perinatal conditions only isolated victoms have mental retardation, the majority being

TABLE 2. *Mean IQ and incidence of mental retardation in low birthweight babies with neonatal neurological signs* (McDonald, 1967)

	Neonatal convulsions or cerebral irritation	No convulsions or cerebral irritation
Mean IQ	101.8	102.4
IQ < 50	6.8%	1.6%

of normal and some of superior IQ, development and achievement. This statement was originally made by Benaran *et al.* (1960), on the results of a follow up of a massive number of babies with perinatal asphyxia. It is equally true of prematurity in which there is no global reduction in IQ in survivors.

This phenomenon has been confirmed by McDonald (1967) for children of very low birthweight even in the presence of alarming neonatal symptoms (Table 2). In even more sinister situations the same consideration

applies. Table 3 shows Illingworth's (1972) report of a prospective study of babies with neural tube defects and Table 4 (Chess *et al.*, 1978) demonstrates the same phenomenon in 243 children with the congenital rubella syndrome.

TABLE 3. *IQ in association with neural tube abnormalities* (Illingworth, 1972)

	Hydrocephaly with spina bifida (240)	Spina bifida without hydrocephaly (113)	Hydrocephaly without spina bifida (122)
IQ > 90	37%	69%	38%
> 80	57%	85%	57%

It is important to acknowledge this fact—that an increased incidence of mental retardation in a given condition does not necessarily or even usually imply any change in modal IQ of the entire group. Otherwise attendants may limit resuscitative effort and care and the proportion—more commonly the majority—of babies of good intellectual calibre or potential may be abandoned or condemned on the grounds of guilt by association with the handicapped minority.

TABLE 4. *Neurological sequelae of congenital rubella syndrome* (Chess *et al.*, 1978)

Normal IQ and behaviour	46.7%
Mental retardation	25.7%
Autism	6.2%

If a few fetal and perinatal causes of mental retardation can operate in isolation—methylmercury poisoning, congenital rubella or toxoplasmosis are examples—for most risk factors there is a much more complex interaction of many of the problems which afflict the fetus and newborn.

The baby afflicted by Rh haemolytic disease provides a ready example. In addition to his haemolytic anaemia he is often subjected to induced labour and prematurity. Assuming that the anaemia is manageable, he still runs the risk of neonatal brain damage from hyperbilirubinaemia. This risk is compounded by prematurity and complications of labour or lack of adequate resuscitation at birth. Not only is the premature baby more vulnerable to kernicterus but in the primate an experimental infusion of bilirubin which will not harm an adequately resuscitated neonate will regularly produce the motor, electroencephalographic and pathological

lesions of kernicterus in a neonate deliberately asphyxiated. Assuming however that obstetric management and neonatal resuscitation are exemplary and that anaemia and hyperbilirubinaemia were expertly managed, there is still the problem of hypoglycaemia. Indeed in our own hospital in simple statistics Rh babies provide more examples of hypoglycaemia than the other two classical situations, the baby of the diabetic mother and the growth retarded baby, put together.

A similar but much less comprehensible and more sinister interaction of factors is seen in socioeconomic deprivation where poor nutrition, high parity, uncertain maturity, a high incidence of low birthweight babies and malformations and obstetric complications of all kinds are finally compounded by poor physical and cultural environment. It is in this sort of multifactorial situation that statistical labels as applied to individual babies become meaningless and that specific obstetric and paediatric terminology, glib explanations of "prematurity" or "birth trauma" or "birth asphyxia", serve more to conceal ignorance than reveal understanding when we have no notion of how the different factors should be measured or weighted.

The following is a selective rather than an exhaustive list of fetal and perinatal conditions wbich are or may be associated with subsequent mental retardation. The criteria for inclusion are either numerical importance or eminent preventability.

1) Neural tube defects. Despite a high diagnosis rate and well recognised epidemiology the cause or causes of neural tube defects remain tantalisingly obscure. An exception is the Meckel-Gruber syndrome, an autosomal recessive.

2) Environmental agents damaging to the embryo and fetus.

a) Infections – rubella, CMV, herpes, toxoplasmosis, syphilis, listeriosis. Of these at least rubella can be reliably prevented by immunisation and maternal syphilis should be diagnosed and treated.

b) Radiation. Usually this is accidental – in the victim of trauma with undiagnosed early pregnancy or in the woman witb typical if unrecognised symptoms of early pregnancy, nausea and urinary frequency, leading to extensive gastrointestinal or renal tract radiological investigations. A more serious dilemma present in tbe rare woman with coexistent neoplastic disease and early pregnancy.

c) Toxic agents:

- maternal antithyroid antibodies;
- atypical maternal pku;

- organic mercury poisoning – methylmercury (Minamata Bay disease);
- maternal alcohol ingestion;
  With the fetal alcohol syndrome as the newest addition to the "lifestyle diseases" it is not known if there is a critical time period for adverse effect or how the rival hazards of a steady intake and an occasional heavy drinking bout compare.

d) Specific dietary deficiency – endemic cretinism.

3) Prematurity, low birth weight, intrauterine growth retardation. Numerous possibilities of handicap and possibilities of interaction of factors exist.

a) the socioeconomic association with prematurity and low birth weight.

b) the reasons for the prematurity or low birth weight.

c) the higher incidence of congenital abnormality.

d) the higher incidence of malpresentations.

e) the greater vulnerability to mechanical and biochemical insults intrapartum.

f) the need for prompt resuscitation at birth.

g) the higher incidence of problems in the neonate coupled with increased vulnerability to many of them:

- respiratory insufficiency;
- hypoglycaemia, hyperbilirubinaemia, hypothermia;
- disturbances of nutrition and electrolytes;
- greater exposure and susceptibility to infection – especially meningitis.

As a clinical generalisation the lowest risk of retardation attends the baby born prematurely for good obstetric reasons (e.g. toxaemia, antepartum haemorrhage, Rh haemolytic disease) followed hy the baby born prematurely for unknown reasons or reasons of fetal choosing (e.g. polyhydramnios, multiple pregnancy, premature rupture of membranes) and the highest risk is assigned to babies of poor weight or nutritional status whatever their maturity at delivery.

4) "Birth trauma" and "birth asphyxia". Birth trauma and birth asphyxia are indispensahle terms, indeed household words, among those who deal with the handicapped. Both terms convey rather sinister implications of obstetric or paediatric incompetence or mismanagement which may or may not be justified. Certainly both terms may be used indiscriminately because in areas of New Zealand with low autopsy

rates on perinatal deaths, there is a significant shortage of deaths from malformation and infection but the discrepancy appears on death certificates as birth trauma or asphyxia.

The real confusion introduced by the term "birth trauma" is that damage is commonly related to the part of the birth process visible to mother and attendants in the delivery. Thus, often in retrospective surveys, apart from birth weight and sex the only information available from the whole of pregnancy, from mother or hospital records, is the fact that the birth was "instrumental" as though this explains everything. Such an attitude ignores entirely the indication for interference be it mechanical obstruction or fetal distress or the protective use of forceps especially for the delivery of the premature head through the perineum.

More serious however is the fact that whether the birth was instrumental or not the mechanical events of the whole of the rest of labour are written off either as unimportant or unfathomable. Cranial compression and deformation in labour can be recognised by bradycardia coinciding in onset peak and disappearance with simultaneous record of contractions but such recognition requires reliable monitors. The common clinical practice of checking fetal heart rates only between contractions can produce highly spurious records of "regular" fetal heart rates. Similarly radiological studies of the mechanics of labour show that moulding, far from being a gentle and gradual process, may be produced very acutely by a single contraction. Again the common radiographic practice in intrapartum pelvimetry of taking films only between contractions can overlook or gravely underestimate the severity of cranial deformation. Both cardiographic and radiologic evidence show that cranial deformation may be episodic at different stages of labour. In this sense birth trauma may be produced early in labour, for instance at the pelvic brim, and events thereafter including the only bit that is recorded—the actual birth—may be irrelevant.

Birth asphyxia and anoxia (strictly hypoxia) are likewise very elastic terms and by their elasticity lose precision. It is now known that as the baby is delivering at the perineum the placenta is separating from the uterine wall and therefore figures for oxygen saturation or CO_2 levels in cord blood, often appalling by adult or paediatric standards, reflect more what has happened in the last 60 or 90 seconds of delivery than the state of affairs throughout labour or pregnancy. Some such reconciliation was necessary because pO_2 measurements on normal babies in utero show that they are not hypoxic and hysteroscopic photographs of the

fetus show that he is pink whereas if cord blood figures at delivery were to be believed he should be cyanosed.

Unfortunately the old notion that the fetus is only one step from death by anoxia—"Mt Everest in utero" still enjoys popular support. It has spawned a variety of medical and paramedical cults from hyperventilation in labour to forced hyperventilation with oxygen in women being anaesthetised for caesarean section and finally commercial enterprises offering women in late pregnancy weekly inhalations of pure oxygen to produce children with superior IQ's. It is in fact difficult to demonstrate that hyperventilation or oxygen breathing makes any difference to fetal oxygenation or, if carried out with the efficiency which anaesthetists can achieve, is just as likely to produce fetal cerebral ischemia from low pCO_2 levels or fetal asphyxia from constriction of the umbilical vessels at high pO_2 levels.

Nevertheless the fetus can be subject to hypoxic or asphyxial experience in pregnancy and labour. Apart from cerebral ischemia and possible trauma from cranial compression already mentioned, two other types of insult can be correlated with characteristic changes in fetal heart rate. Impaired uteroplacental exchange produces bradycardia or dips in fetal heart rate starting late in contractions and outlasting the contractions while cord compression produces a variable bradycardia with no consistent relationship to contractions.

Cord prolapse is an interesting condition because by conventional textbook descriptions this is a condition where the cord can be palpated in the cervix or in more extreme cases the cord snakes out into the vagina or even through the vulva. This accident is most common with transverse lies, next commonest in breeches, but rarest with cephalic presentations which is considered tbe reverse order of seriousness for the fetal head is an efficient compressor but the transverse lie is not. This benign assumption may not be justifiable for the appearance of the cord at amniography is very different from the appearance in the kidney dish after delivery. The cord in utero is not a slack and sloppy catenary but with the high blood flow through the umbilical vessels dances like a snake. It is virtually erectile tissue and there is good reason to accept the argument that a baby must already be bypotensive for a cord to prolapse as the normal cord is too stiff to prolapse. A much more common finding at intrapartum amniography or caesarean section is the occult cord prolapse, the loop of cord lying alongside the head and subject to compression.

The baby either dies or does not. In either case as labour progresses the cord is left behind perhaps as a loop around the fetal neck. If the baby

survives the episode is forgotten or goes unrecognised. If the baby is stillborn "cord around neck" is gravely reported as the cause of fetal death and in either case we are left with the same conclusion as with "birth trauma"—"birth asphyxia" is what happens or is found at delivery ignoring the insults to which the baby has been subject in pregnancy and the rest of labour.

The fact that asphyxial experience in pregnancy and labour may have been episodic and ignorance of the duration of asphyxia of the baby depressed at birth make for much confusion in both retrospective and prospective studies. In the primate fetus it has been shown that acute total asphyxia produces brain stem lesions and failure of neonatal respiration. However prolonged subacute asphyxia produces cerebral oedema and a pattern of hemispheral chronic histological lesions with motor, learning and behavioural disorders more characteristic of human "birth asphyxia" babies. In this context it is worth noting that occasional babies stillborn from apparently acute hypoxia have been successfully resuscitated by prompt ventilation and cardiac massage with subsequent normal development or minimal handicap. Conversely and more commonly babies in reasonable condition at birth may show subsequent cerebral handicap which is either inexplicable or arbitrarily assigned to " instrumental birth".

It is commonly assumed by those who do not have to do caesarean sections that delivery by caesarean section is a safe and easy way for a baby to be born and that birth trauma and birth asphyxia could always be avoided. It is true that many caesarean sections like many vaginal deliveries are simple and straightforward although tentorial tears, a classical example of birth trauma, are occasionally seen in babies delivered by elective caesarean section. However the real fallacy lies in the benign assumption that the delivery that would have been difficult or dangerous by the vaginal route will be an easy caesarean section. Breeches, transverse lies and well engaged or impacted heads make for difficult and traumatic caesarean sections in unskilled hands and in other situations—fetal distress, cord accidents, placenta praevia—prompt and efficient resuscitation of the baby is essential if the technical expertise of caesarean section is not to be wasted.

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MENDELIAN CAUSES OF SEVERE MENTAL DEFICIENCY

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INTRODUCTION

The following report is an attempt to determine the genetic load of the Mendelian causes (dominant, recessive and x-linked) of mental deficiency. Because of the lack of exact information and essential data, this report should be considered a rough estimate or approximation of the total problem and, by necessity, the data included in this report will be an underestimation of the total amount of genetic causes producing mental deficiency. The report is a summary of various studies on the genetic causes of mental deficiency in children. Using data in childhood does not give adequate representation of what is happening because there will be fetuses and infants dying of genetic causes which go undiagnosed; brain damage in newborns and infants, where the death rate is high may go undetected; and studies during childhood will miss mental deficiency coming on in adult life. Data during childhood is used because it represents the most accurate information available even though it is incomplete. The information in this report is based upon presently known genetic causes of mental deficiency and does not compensate for the fact that additional genetic diseases will be discovered in the future.

In an attempt to produce some reliable estimate of the amount of mental deficiency produced by Mendelian genetic factors, the report will concentrate on severely mentally deficient children—those having an Intelligence Quotient (I. Q.) below 50 and who frequently have associated physical abnormalities. The decision to use the severely mentally deficient group for the estimates of the genetic causes of mental deficiency is based on the following:

a) There is a body of genetic data on this group that most researchers would accept as reliable for analysis.

b) There is agreement that the prevalence of severe mental deficiency is 4 per 1,000 children and that the condition seems to be fairly constant in frequency and type in various populations.

c) Approximately 21.5 to 35 percent of all the cases of severely retarded children are caused by Mendelian genetic factors.

d) There are fairly good estimates of the percentage of children having severe mental deficiency which are caused by dominant, recessive and x-linked genetic factors.

In order to better understand the etiological causes of severe mental deficiency, the numerical proportions of this group to the total problem of mental deficiency, and genetic components producing severe mental deficiency, this paper will first make some general observations on the total problem of mental deficiency.

It is generally accepted that during childhood the prevalence of mental deficiency is 3 percent (30 per 1,000 children). Of this total, severe mental retardation during childhood has a mean of 0.4 percent, 4 per 1,000 children. The frequency and types of severe mental deficiency seem to be fairly constant in most populations. Mild mental deficiency is approximately 8-10 times more common than severe mental deficiency. It is important to note that the etiological causes, as well as the genetic factors and associated physical abnormalities which may accompany severe mental deficiency, are quite different in the mildly mentally deficient population.

The mean I.Q. curve for a population is considered to be 100 and the Standard Deviation (S.D.) is about 15. In general, the population with an I.Q. range of 85 to 115 would be within 1 S.D. of the mean and would contain about 67 percent of the population. An I.Q. range of 70 to 130 would be within 2 S.D. of the mean and would contain 96 percent of the population. The I.Q. curve is skewed to the left. While Gaussian expectations suggest that 2.27 percent of the population would have an I.Q. of less than 70, the percentage in this population during childhood is 3 percent. The data suggest that the cause of severe mental deficiency, in many or most individuals, is not the same cause encountered in those in the high I.Q. range of mental deficiency. It has to be emphasized that while the I.Q. is a useful tool during childhood to characterize the magnitude of the problem of mental deficiency, it is not the only way of evaluating mental deficiency. The I.Q. score has to be used with many reservations and careful consideration has to be given when dealing with particular populations. The safest principle is to assume that every child has the potential for intellectual development, until proven otherwise.

In the severe mental deficiency group, there are many physical and psychomotor indicators suggesting mental deficiency, other than the I.Q. score.

The distinction between mild and severe mental deficiency is of value not only on a statistical basis but also on a biological and etiological basis. In general, the severely mentally deficient have many more physical and central nervous system abnormalities than the mildly mentally deficient.

Factors such as growth retardation, reduced head circumference, brain deformities, convulsions, seizures, spasticity, congenital heart abnormalities, etc. occur much more frequently in severe mental deficiency. In the latter, single cases in families are usual and all groups within a society seem to be equally involved.

In a Swedish study of mild mental deficiency among 93 school children with an I.Q. between 50-70, a third of the children were diagnosed as having a known genetic cause. Four percent were due to a chromosomal abnormality and 31 percent were due to polygenic inheritance. A recognized syndrome was present in 2 percent of the children and a prenatal factor was present in 8 percent. In the latter group, maternal alcoholism was a major etiological factor. A perinatal cause was found in 16 percent and a postnatal cause in 2 percent. Psychoses occurred in 2 percent and an unknown etiology in 28 percent. An abnormal psychiatric status was present in 30 percent of the children, epilepsy in 10 percent, cerebral palsy in 8 percent and clumsiness in 23 percent.

General comments on severe mental deficiency (SMD)

In severe mental deficiency, the I.Q. is 50 or below. The mean prevalence rate is 4 per 1,000 children (range 2.8 to 5.4 per 1,000). It has been estimated that between 1-2 percent of all newborn infants are potentially retarded. Affected newborns with an I.Q. of less than 25 will have a 90 percent mortality rate within the first 5 years of life. Survival figures for this group of infants will vary greatly depending on the type of medical services that are available at the time of birth and during infancy and early childhood. For the I.Q. range of 25-30, the mortality rate is less, approximately 50 percent during the first 5 years of life. In adults age 20 years and older, severe mental deficiency occurs much less frequently than in childhood, at approximately .04 per 1,000 adults. This marked reduction in prevalence of severe mental deficiency in adults is a reflection of the high death rate that occurs in this population starting in early infancy and childhood.

Severe mental deficiency can be divided generally into the following etiological groups: those produced by Mendelian genetic factors represent the largest group and account for 21.5-35 percent of all the cases; chromosomal abnormalities 20 percent; exogenous factors 30 percent; and unknown causes 10 to 15 percent (see Table 1).

TABLE 1. *Causes of severe mental deficiency*

	Percent*
Genetic	21.5-35
Chromosome	20
Exogenous	30
Unknown	10-15

* Figures do not add up to 100 percent, since they represent a summation of various studies.

Genetic Mendelian traits which account for 21.5-35 percent of all the individuals with severe mental deficiency are represented in the following proportions, namely, dominant traits account for 21 percent, recessive traits, which are exactly double the dominant traits, account for 42 percent and x-linked traits, 37 percent. In terms of the total numbers of severely mentally deficient children, dominant traits account for 4.5 percent of the individuals, recessive traits 9 percent and x-linked 8 percent (see Table 2).

TABLE 2. *Mendelian causes of severe mental deficiency (SMD)*

	Percentage of genetic causes	Percentage of all causes of SMD
Dominant	21	4.5
Recessive	42	9
X-linked	37	8
Total	100	21.5

CHROMOSOME ABNORMALITIES

Chromosome abnormalities account for approximately 20 percent of the severe mentally deficient population. This group will be presented in a separate paper and, therefore, it will not he discussed further in this report.

Early prenatal abnormalities

Early prenatal abnormalities account for approximately 13 percent of the severely mentally deficient population. It is a poorly defined group and contains such known conditions as neural tube defects, deLange, Rubinstein-Taybi, and tbe Sturge-Weber syndromes, cerebral gigantism, hypercalcemia, dwarfism and skull abnormalities. Not much is known about the causes of these defects but the causes may include teratogens and detrimental environmental agents, chromosomal deletions or rearrangements, fresh mutations, and polygenic and multifactorial genetic factors. In the future, many individuals in tbis diagnostic category will be reclassified, as we learn more about the causes of mental deficiency.

Perinatal factors

Perinatal factors account for approximately 10 percent of severe mental deficiency. As yet, it is difficult to be certain about the cause and effect relationship of severe mental deficiency and unusual events occurring during the perinatal period. As more is learned about fetal placental development, maternal nutrition, neonatal oxygen, nutritional and environmental needs of the fetus and neonate, we should bave a better understanding about how the fetus or neonate can be damaged during this period of development. Perinatal factors producing severe mental defiiciency include prematurity, subdural and central nervous system hemorrhage, hypoglycemia, hydrocephalus, hypothyroidism and many other such diagnoses.

Perinatal and postnatal infections

Perinatal and postnatal infections account for approximately 13 percent of severe mental deficiency. Tbe two conditions are nearly equally divided in frequency with perinatal infections occurring slightly more frequently, by 1-2 percent. Included in this group are such conditions as rubella, cytomegalic inclusion disease, meningitis, encephalitis, gastroenteritis and septicemia.

Deprivation and injuries

Deprivation and injuries account for approximately 2 percent of severe mental retardation. Included in this category are such conditions as accidental head injury, poisoning and toxins (alcoholism), battered babies, maternal prenatal trauma, starvation and nutritional deficiency.

Unknown causes

This category accounts for approximately 21 percent of severe mental deficiency. With a better understanding of mental deficiency and its causes, an exact diagnosis could be made and the patients classified under one of the other headings.

Mendelian genetic factors

Mendelian genetic causes, in general, are a factor in approximately one-third of all the patients with severe mental deficiency. The range during childhood is between 21.5 and 35 percent. In one reported series of severe mental deficiency, of the total number of patients, dominant traits accounted for 4.5 percent, recessive traits 9 percent and x-linked traits 8 percent. Using the same reported series of cases but limiting the percentages to the total number of Mendelian genetic cases, the dominant traits accounted for 21 percent of the cases, recessive traits 42 percent and x-linked traits 37 percent (see Tables 1 and 2).

Dominant conditions

Genetically dominant diseases account for approximately 4.5 percent of all the patients with severe mental deficiency. This is undoubtedly an underestimation but is the best approximation presently available. This could be an underestimation by as much as 1-3 percent. There are still many diseases producing severe mental retardation which are not diagnosed and could be caused by a dominant trait; there are others that exist in the population only by fresh mutations which present difficulty in identification. While many of the dominant conditions in this category are due to fresh mutations, each individual dominant disease has its own mutation rate.

For example, in epiloia, or tuberous sclerosis, the inherited form of the disease accounts for 50 percent of the patients, while the disease caused by fresh mutations accounts for the additional 50 percent of the patients. In those dominant diseases where the fertility of the affected individual is low, fresh mutations will account for the majority of new cases. In those dominant diseases where the expressivity of the abnormal gene varies greatly, an increasing number of patients will be accounted for by the inherited form of the abnormal gene.

Each dominant disease has its own ratio of fresh mutations to the inherited form of the disease which has to be taken into consideration

when evaluating methods of prevention. Some of the more common dominant diseases in this category are Noonan's syndrome, tuberous sclerosis, neurofibromatosis, cleidocranial dysostosis, Crouzon's and Aperts' syndromes.

Recessive conditions

Recessive diseases account for approximately 9 percent of severe mental deficiency. This category contains many causes of severe mental deficiency. The diseases in this group range from individuals with severe physical abnormalities to individuals with major biochemical defects. It is to be expected that the types of diseases in this category will vary from country to country and among different populations. Within this group of diseases, there would be an increased incidence of incest, consanguinity, first-cousin marriages and population inbreeding. Some of the diseases in this category are cerebral degenerative disorders, phenylketonuria, Smith-Lemni-Opitz syndrome, mucopolysaccharidosis, homocystinuria, hyperglycinemia, familial microcephaly, Sjögren-Larsson syndrome, Seckel dwarfism and familial spastic diplegia.

X-Linked conditions

X-linked conditions account for approximately 8 percent of severe mental deficiency. The incidence of x-linked diseases producing mental deficiency in males can vary among populations. For example, in New South Wales, 20 percent of the moderately retarded males were thought to be affected by an x-linked form of mental deficiency. It is to be expected that the types of x-linked mental retardation will vary greatly among populations and the following are but a few examples of x-linked diseases occurring in a particular population: Renpenning, Lesch-Nyhan and Borjeson Forssman syndromes, Duchenne muscular dystrophy and some forms of hydrocephalus.

Genetic comments

In 1977, Newton et al. reanalyzed Penrose's classical 1938 Colchester report on mental deficiency. The authors estimated that about 351 autosomal loci are capable of producing mental deficiency and that there is an inbred load of 0.83 detrimental equivalents. They concluded that there was a mutation rate of 0.008 per gamete or less than 2.4×10^{-5} per loci.

Dominant conditions

Difficulty exists in determining the genetic load and fresh mutation rates, since different diseases have their own characteristics. In addition, modifying factors, which will be discussed later, vary among diseases. In spite of these limitations, some general principles can be put forth. Fresh mutation rates vary for different loci on the chromosomes. The range seems to be about 1:10,000 (1×10^{-4}) to 1:1,000,000 (1×10^{-6}) per locus per gamete per generation, with the average being 1:100,000 (1×10^{-5}). The method of measurement of a dominant mutation is n/2N where n is the number of patients born to normal parents over a defined time span and N is the total number of normal births during the same time. Since a dominant trait requires a mutation in only one of two gametes, n/N is multiplied by 1/2. As an example of determining the fresh mutation rate, epiloia, which is due to a dominant gene, occurs in the general population in England with a frequency of one in 30,000. It has been estimated in England that half of the patients are the result of fresh mutations and the other half are caused by an inherited form of the abnormal gene. The fresh mutation rate, therefore, is $1/2 \times 1/30{,}000 \times 1/2$ or one in 120,000, or 8 per million gene loci per generation.

It is important to identify the heterozygote parent of an epiloic patient, since the inherited form of the disease seems to vary in frequency in different populations. In England, the inherited form of the disease occurs in 50 percent of the patients but in another population it has been estimated to occur in as low as 15 percent of the patients.

In estimating fresh mutation rates, allowance must be made for genetic heterogeneity of the disease, underascertainment of patients, unclassified parents and reduced penetrance. If the same disease (phenotype) can be produced by a mutation at more than one locus or an environmental factor can mimic the disease, the accurate determination of mutation rate becomes difficult.

Severe mental deficiency is associated with a low fertility rate and, among those individuals with an I.Q. below 25, there is almost complete absence of fertility, usually due to both physical and social causes. Diseases, such as epiloia, demonstrate marked heterogeneity so that an inherited form of the disease is present with one parent having only minor physical manifestation of the disease and fertility in general is not diminished. In spite of this, many dominantly inherited diseases are rarely found in more than two generations as exemplified by epiloia. Severe mental de-

ficiency is maintained in the population by the inherited form of the abnormal gene and the fresh mutation rate. Certain diseases suspected of being due to a dominant trait are still difficult to classify, since the fresh mutation rate represents 100 percent of the patients and the inherited form of the disease is not found.

Recessive traits

The problem of determining accurate mutation rates and genetic load is much more difficult when evaluating recessive traits. In general, the types and frequencies of recessive diseases producing mental deficiency vary greatly among different populations of the world. Recessive mental deficiencies depend upon the presence of two precisely similar genes, one gene coming from each parent. The homozygous mentally deficient individual has normal parents, both heterozygous for the gene producing the mental deficiency.

Recessively transmitted traits producing mental deficiency are usually severe and the manifestations vary less from patient to patient than do dominant abnormalities. Natural selection acts slowly against recessive diseases because the heterozygous carrier is usually not abnormal, even though the homozygote may be infertile and have a markedly reduced life span. Occasionally, the heterozygote carriers may manifest mild signs of the recessive trait and these signs are inherited as irregular dominant characters.

In general, recessive genes producing mental deficiency are most likely due to inheritance rather than being the result of a fresh mutation. General conclusions are difficult to apply when evaluating the genetic load for recessive causes of mental deficiency. For example, for different populations, the types of recessive genes producing mental deficiency will vary and the gene frequency among populations for similar diseases can be quite different. As seen in Tay Sachs disease, the gene frequency of non-Ashkenazi individuals is ten times less than the Ashkenazi Jewish population. Cultural and other local customs will also influence the number of mentally deficient individuals in the population that are caused by recessive genes. Factors such as consanguinity or the ability to marry a cousin or close relative has a small but measurable effect on the difference in the occurrence of mental deficiency seen among different populations. Genetic isolates for rare recessive genes producing mental deficiency will also increase the number of abnormal individuals being produced. Under these circumstances, the abnormal gene frequency in the isolate group will be con-

siderably higher than for the general population. It is quite difficult to determine if the recessive genes are in equilibrium in the population. Many believe that for most recessive genes, equilibrium has not been reached nor will it occur for a long time. Under certain circumstances, if the heterozygous carriers are endowed with even a minute advantage in fertility, as compared with the general population, a sort of genetic equilibrium can be maintained, even though infertility occurs in the homozygote. This fact makes the mutation rate of genes causing recessive mental deficiency difficult to estimate even in populations where the degree of inbreeding is constant.

X-LINKED GENES

Presently there are 32 loci on the X chromosome which can produce mental deficiency and, in the near future, the number will probably double. The 32 loci produce a mixture of both mild and severe mental deficiency. It is significant that this one chromosome is estimated to produce 8 percent of the total number of patients representing all causes of severe mental deficiency, even though the haploid X chromosome accounts for only 4.6 to 6 percent of all the chromosome material.

It has been estimated that the mutation rate *per X chromosome* is 58×10^{-5}. This is predicated on the assumptions that the fertility of affected males (hemizygotes) is negligible, but in carrier females (heterozygotes), it is normal and that mutation is equally frequent in the egg and sperm. For recessive X-linked loci producing severe mental deficiency, the mutation rate per locus is approximately 3.2×10^{-5}, a fairly typical mutation value. The ratio of the detrimental gene being passed through a carrier female to an affected male to a fresh mutation of a locus on the X chromosome of an egg or sperm varies with different diseases.

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I wish to thank Professor Sewell Wright for his helpful discussion on genetic load.

NATALITY, GENERAL MORTALITY AND NATURAL INCREASE

ABSOLUTE NUMBERS AND CRUDE RATES PER 1 000 POPULATION

Country or area		Natality (live-born)					General mortality					Natural increase
		Code*	Number			‰	Code*	Number			‰	‰
			T	M	F	T		T	M	F	T	T
Africa												
Algeria	1976	C	670 603	342 714	327 389	38.8	U	163 942	89 224	74 718	9.5	29.3
Angola	1973	U	126 125	60 352	66 173	21.5	U	16 322	10 117	6 205	2.8	18.7
Cape Verde	1975	C	8 210	4 092	4 118	27.6	C	2 796	1 376	1 420	9.4	18.2
Comoros	1970	...	11 783	...	...	43.5	...	5 284	...	...	19.5	24.0
	1973	...	8 700	...	...	30.7	...	...	...	...	...	...
Djibouti	1970	U	3 991	...	...	42.0	U	724	...	...	7.6	34.4
Egypt	1975	C	1 403 877	...	...	37.7	C	456 041	...	...	12.2	25.4
	1976	...	...	...	...	...	...	...	...	...	...	...
	1977	C	1 460 620	...	...	37.7	C	457 329	...	...	11.8	25.9
Guinea-Bissau	1971	U	7 906	4 284	3 622	16.3	U	1 044	705	339	2.1	14.1
Kenya	1974	U	236 661	...	...	18.3	U	53 335	...	...	4.1	14.2
	1975	...	...	...	...	...	...	...	...	...	...	...
	1976	U	277 000	...	...	20.0	U	50 000	...	...	3.6	16.4
Lesotho	1974	...	37 293	18 806	18 487	36.7	...	14 751	7 684	7 077	14.5	22.2
Liberia	1971	...	78 301	40 686	37 615	52.3	...	24 990	13 580	11 410	16.7	35.6
Libyan Arab Jamahiriya	1975	U	115 968	59 249	56 719	47.7	U	17 118	9 628	7 490	7.0	40.7
	1976	U	119 863	61 059	58 804	47.7	U	17 450	9 883	7 567	6.9	40.8
Madagascar	1972	U	274 665	140 772	133 893	34.1	U	81 760	42 611	39 149	10.3	23.8
Malawi	1972	...	208 179	101 589	106 590	50.5	...	109 223	55 788	53 435	26.5	24.0
Mauritius	1976	C	22 250	11 256	10 994	25.6	C	6 815	3 975	2 840	7.9	17.7
	1977	C	22 730	11 600	11 130	25.8	C	6 966	4 073	2 893	7.9	17.9
Mozambique	1975	U	61 563	32 894	28 669	6.7	U	13 705	8 173	5 532	1.5	5.2

* Code used by the Statistical Office of the United Nations, New York: Civil registration data said to be relatively complete are coded "C", those said to be unreliable (incomplete) are coded "U".

Country or area		Natality (live-born)					General mortality					Natural increase
		Code*	Number			‰	Code*	Number			‰	‰
			T	M	F	T		T	M	F	T	T
Réunion	1974	C	13 356	...	...	28.1	C	3 085	...	...	6.5	21.6
	1975	C	13 277	...	...	26.5	C	3 175	...	...	6.3	20.2
	1976	...	...	...	...	...	...	...	...	...	...	...
	1977	C	12 544	...	...	25.7	C	3 105	...	...	6.3	19.4
Rwanda	1975	U	109 522	...	...	26.1	U	31 935	...	...	7.6	18.5
St. Helena (Excluding dependencies)	1976	...	104	46	58	20.0	...	54	29	25	10.4	9.6
São Tomé and Principe	1973	C	3 033	1 552	1 481	38.9	C	993	514	479	12.7	26.2
Seychelles	1977	C	1 599	...	...	25.9	C	477	...	...	4.7	21.2
South Africa	1970/1975	...	...	...	...	42.9	...	...	...	...	15.5	27.4
Southern Rhodesia	1976	...	19 365	...	...	3.0	...	15 773	...	...	2.4	0.6
Togo	1970	U	73 306	...	...	39.4	U	14 364	...	...	7.7	31.7
Tunisia	1976	C	208 724	...	...	36.4	C	35 919	...	...	6.3	30.1
Western Sahara	1974	U	1 641	...	...	15.2	U	317	...	...	2.9	12.3
Zaire	1974	...	1 129 962	...	...	46.6	...	451 741	...	...	18.6	28.0
America												
Antigua	1977	C	1 429	...	...	19.8	C	489	...	...	6.8	13.0
Argentina	1970	C	544 521	276 206	268 315	22.9	C	222 113	130 731	91 382	9.4	13.5
Bahamas	1976	C	5 295	2 349	2 458	24.7	C	976	534	442	4.6	20.1
Barbados	1976	C	4 593	2 300	2 293	18.6	C	2 343	1 143	1 200	9.4	9.2
Belize	1975	U	5 201	2 678	2 523	37.2	U	723	371	352	5.2	32.0
Bermuda	1975	C	837	416	421	15.0	C	398	231	167	7.1	7.9
	1976	C	856	418	438	15.2	C	384	226	158	6.8	8.4
Bolivia	1976	U	117 017	...	...	20.2	U	26 841	...	...	4.6	15.6
Brazil	1975	...	4 243 858	2 112 901	2 130 957	39.6	...	828 446	478 459	349 258	7.7	31.9
	1976	...	5 676 120	...	...	51.5	...	843 326	...	...	7.7	43.8
British Virgin Islands	1975	C	215	101	114	19.5	C	65	35	30	5.9	13.6
Canada	1976	C	364 630	...	...	15.8	C	166 490	...	...	7.2	8.6
	1977	C	360 340	...	...	15.5	C	169 040	...	...	7.2	8.3
Cayman Islands	1976	U	282	...	...	20.1	U	81	...	...	5.8	14.3
Chile	1976	C	249 753	...	...	23.9	C	79 389	42 975	36 414	7.6	16.3
Colombia	1976	U	731 163	...	...	30.0	U	219 300	...	...	9.0	21.0
Costa Rica	1976	C	59 965	...	...	29.7	C	9 356	5 240	4 116	4.6	25.1
Cuba	1976	C	187 555	...	...	19.8	C	52 907	30 240	22 667	5.6	14.2
Dominica	1977	C	1 745	...	...	21.8	C	532	...	...	6.7	15.1
Dominican Republic	1975	U	161 618	82 281	79 337	34.4	U	25 541	13 876	11 665	5.4	29.0

Ecuador	1974	U	244 530	123 470	121 060	35.2	U	64 278	33 368	30 910	9.2	26.0
	1975	U	221 209	112 589	108 620	31.3	U	55 053	28 823	26 230	7.8	23.5
El Salvador	1976	C	165 822	84 186	81 636	40.2	C	30 826	17 433	13 393	7.4	32.8
Falkland Islands (Malvinas)	1976	C	36	18	18	18.9	C	10	6	4	5.3	13.6
	1977	C	35	15	20	18.9	C	28	17	11	15.1	3.8
French Guiana	1974	U	1 533	...	...	30.4	U	420	...	...	8.3	22.1
	1975	U	1 474	...	...	24.6	U	402	...	...	6.7	17.9
	1976	...	...	...	...	...	...	...	...	...	...	...
	1977	U	1 463	...	...	24.4	U	452	...	...	7.5	16.9
Greenland	1976	C	859	454	405	17.3	C	348	214	134	7.0	10.3
Grenada	1975	C	2 890	1 453	1 437	27.4	C	687	338	349	6.5	20.9
Guadeloupe	1974	C	8 842	...	...	26.2	C	2 394	...	...	7.1	19.1
	1975	C	8 254	...	...	23.3	C	2 315	...	...	6.5	16.8
	1976	...	...	...	...	...	...	...	...	...	...	...
	1977	C	6 320	...	...	17.3	C	2 265	...	...	6.2	11.1
Guatemala	1976	C	266 497	...	...	42.6	C	61 251	...	...	9.8	32.8
Guyana	1976	C	20 861	...	...	26.7	C	5 540	...	...	7.1	19.6
Haiti	1972	...	137 621	...	...	27.1	...	69 109	32 683	36 426	13.6	13.5
Honduras	1976	U	132 793	67 931	64 862	46.9	U	18 168	9 796	8 372	6.4	40.5
Jamaica	1976	C	61 357	...	...	29.3	C	14 671	...	...	7.1	22.2
	1977	C	61 021	...	...	28.8	C	14 245	...	...	6.8	22.0
Martinique	1974	C	7 290	...	...	21.2	C	2 346	...	...	6.8	14.4
	1975	C	6 709	...	...	18.5	C	2 270	...	...	6.3	12.2
	1976	...	...	...	...	...	...	...	...	...	...	...
	1977	C	5 409	...	...	14.5	C	2 155	...	...	5.8	8.7
Mexico	1976	U	2 156 430	...	...	34.6	C	406 033	...	...	6.5	28.1
Montserrat	1974	C	304	150	154	24.9	C	131	58	73	10.7	14.2
	1975	C	213	103	110	17.5	C	128	52	76	10.5	7.0
	1976	C	206	108	98	16.9	C	128	64	64	10.5	6.4
	1977	C	205	92	113	15.8	C	138	63	75	10.6	5.2
Netherlands Antilles	1973	U	4 405	2 261	2 144	19.9	U	1 061	567	494	4.8	15.1
Nicaragua	1973	U	79 380	...	...	39.4	U	13 324	...	...	6.6	32.8
	1974	...	...	...	...	...	U	10 574	5 856	4 718	5.1	...
	1975	...	...	...	...	...	U	11 143	6 182	4 961	5.2	...
Panama	1976	C	50 667	...	...	29.5	U	8 169	...	...	4.8	24.7
	1977	C	51 084	...	...	28.8	U	8 508	...	...	4.8	24.0
Canal Zone	1976	C	539	284	255	12.9	C	84	56	28	2.0	10.9
	1977	C	561	...	...	14.8	C	75	...	...	2.0	12.8
Paraguay	1976	U	23 157	...	...	8.5	U	13 791	7 279	6 512	5.1	3.4
Peru	1973	U	506 185	260 007	246 178	34.6	U	134 104	69 730	64 374	9.2	25.4
Puerto Rico	1977	C	76 091	...	...	23.0	C	18 905	...	...	5.7	17.3
St. Kitts-Nevis-Anguilla	1976	C	1 320	686	634	27.2	C	476	...	...	9.8	17.4
St. Lucia	1976	C	4 095	...	...	34.8	C	883	...	...	7.5	27.3
St. Pierre and Miquelon	1974	C	97	49	48	16.6	C	53	31	22	9.1	7.5

Country or area		Natality (live-born)					General mortality					Natural increase
		Code*	Number			‰	Code*	Number			‰	
			T	M	F	T		T	M	F	T	T
St. Vincent	1973	C	3 243	...	...	34.4	C	990	...	...	10.0	24.4
Suriname	1966	C	12 925	...	...	40.9	C	2 280	...	...	7.2	33.7
Trinidad and Tobago	1976	C	27 762	14 075	13 687	25.3	C	7 571	4 005	3 566	6.9	18.4
	1977	C	27 094	13 844	13 250	...	C	7 275	3 848	3 427	...	...
Turks and Caicos Islands	1975	...	159	77	82	26.5	...	54	28	26	9.0	17.5
United States of America	1976	C	3 165 000	...	...	14.7	C	1 909 440	1 051 983	857 457	8.9	5.8
	1977	C	3 313 000	...	...	15.3	C	1 898 000	...	...	8.8	6.5
United States Virgin Islands	1976	C	2 530	...	...	26.5	C	512	...	...	5.4	21.1
Uruguay	1975	C	58 830	28 920	29 910	19.2	C	27 437	15 280	12 157	9.0	10.2
	1976	C	59 190	...	...	21.1	C	28 838	16 219	12 619	10.3	10.8
Venezuela	1976	U	455 036	...	...	36.8	U	76 668	42 568	34 100	6.2	30.6
Asia												
Bahrain	1976	...	8 984	4 511	4 478	40.0	...	1 055	...	...	4.7	35.3
Brunei	1977	C	5 397	...	...	28.4	C	746	...	...	3.9	24.5
Burma	1972	U	171 790	...	...	39.0	U	52 290	...	...	11.9	27.1
Cyprus	1976	...	12 495	6 532	5 963	19.6	...	6 240	3 240	3 000	9.8	9.8
Democratic Kampuchea	1969	...	280 198	...	...	41.8	...	133 428	...	...	19.9	21.9
Democratic Yemen	1967	C	7 114	...	...	27.5	C	1 735	...	...	6.7	20.8
East Timor	1972	U	11 311	6 472	4 839	17.8	U	7 950	4 493	3 457	12.5	5.3
Hong Kong	1977	C	78 807	40 793	38 014	17.5	C	23 459	12 824	10 635	5.2	12.3
India	1971	...	7 651 167	4 016 842	3 634 325	36.9	...	2 633 477	1 419 045	1 214 432	14.9	22.0
Indonesia	1964	...	2 983 617	1 537 444	1 446 173	30.6	...	902 244	517 367	384 877	9.2	21.4
Iran	1976	U	1 402 000	725 000	677 000	41.7	U	155 000	109 000	46 000	4.6	37.1
Iraq	1975	U	192 328	100 656	91 572	17.3	U	51 755	29 332	22 423	4.7	12.6
Israel	1976	C	98 763	50 686	48 077	28.0	C	24 012	13 141	10 871	6.8	21.2
	1977	C	94 200	...	...	26.1	C	24 644	...	...	6.8	19.3
Japan	1976	C	1 832 617	943 829	888 788	16.3	C	703 270	378 630	324 640	6.3	10.0
	1977	C	1 755 100	903 380	851 720	15.5	C	690 074	372 175	317 899	6.1	9.4
Jordan	1975	C	83 882	...	...	31.0	U	7 402	4 459	2 943	2.7	28.3
	1976	C	84 380	44 063	40 317	30.4	U	7 383	...	...	2.7	27.7
Kuwait	1976	C	46 039	23 465	22 574	43.3	C	4 661	2 805	1 856	4.4	38.9
Lao People's Dem. Rep.	1971	...	139 214	70 453	68 761	45.9	...	68 126	34 477	33 649	22.5	23.4
Lebanon	1973	U	74 837	...	...	24.5	U	13 052	...	...	4.3	20.2
Macau	1975	...	2 583	1 296	1 287	9.5	...	1 398	752	646	5.2	4.3
Malaysia:												
Peninsular Malaysia	1974	U	312 740	160 652	152 088	32.1	U	64 000	36 893	27 107	6.6	25.5
	1975	U	313 741	160 844	152 897	31.4	U	64 360	37 033	27 327	6.4	25.0

Sabah	1974	U	26 798	13 912	12 886	33.9	U	3 385	1 976	1 409	4.3	29.6
	1975	U	29 115	15 040	14 075	35.5	U	3 510	2 060	1 450	4.3	31.2
Sarawak	1975	U	32 240	16 810	15 430	29.2	U	5 470	3 219	2 251	5.0	24.2
Maldives	1974	...	5 002	2 602	2 400	38.9	...	2 230	1 173	1 057	17.3	21.6
	1975	...	5 232	2 714	2 518	39.8	...	1 386	728	658	10.5	29.3
	1976	...	6 131	3 139	2 992	45.3	...	1 565	806	759	11.6	33.7
Mongolia	1970	...	50 100	...	...	40.2	...	15 300	...	...	12.3	27.9
Pakistan	1968	...	1 604 337	...	...	36.4	...	530 492	282 626	247 866	12.0	24.4
Philippines	1975	U	1 223 837	638 237	585 600	28.8	U	271 136	153 505	117 631	6.4	22.4
Singapore	1977	C	38 364	19 917	18 445	16.6	C	11 955	6 962	4 990	5.2	11.4
Sri Lanka	1972	C	384 066	...	...	29.5	C	100 080	...	...	7.7	21.8
Syrian Arab Republic	1975	U	361 183	179 421	181 762	49.1	U	41 879	23 665	18 214	5.7	43.4
	1976	U	345 356	173 160	172 196	45.5	U	42 083	23 691	18 392	5.5	40.0
Thailand	1976	U	1 166 292	598 809	567 483	28.4	U	237 062	135 595	101 467	5.7	22.7
	1977	U	1 156 504	595 333	561 171	26.3	U	236 783	134 777	102 006	5.4	20.9
Europe												
Albania	1971	C	72 784	37 598	35 186	33.3	C	17 768	9 307	8 461	8.1	25.2
Andorra	1976	...	469	...	...	16.5	...	143	...	...	5.0	11.5
Austria	1977	C	85 595	43 978	41 617	11.4	C	92 402	44 522	47 880	12.3	0.9
Belgium	1976	C	120 472	61 880	58 592	12.3	C	118 765	62 234	56 531	12.1	0.2
	1977	C	121 523	62 274	59 249	12.2	C	112 208	58 979	53 229	11.3	0.9
Bulgaria	1976	C	144 929	74 682	70 247	16.5	C	88 348	47 739	40 609	10.1	6.4
	1977	C	141 723	...	...	16.1	C	94 362	51 111	43 251	10.7	5.4
Channel Islands:												
Guernsey	1976	C	623	326	297	11.6	C	606	301	305	11.3	0.3
Jersey	1976	C	786	398	388	10.6	C	900	477	423	12.1	−1.5
Czechoslovakia	1977	C	281 722	144 765	136 957	18.7	C	173 006	91 286	81 720	11.5	7.2
Denmark	1976	C	65 267	33 734	31 533	12.9	C	53 745	29 080	24 665	10.6	2.3
	1977	C	61 878	31 823	30 055	12.2	C	50 172	27 293	22 879	9.9	2.3
Faeroe Islands	1976	C	756	382	374	18.3	C	292	173	119	7.1	11.2
Finland	1975	C	65 719	33 817	31 902	13.9	C	43 853	23 916	19 937	9.3	4.6
	1976	C	66 846	34 306	32 540	14.1	C	44 786	24 443	20 343	9.5	4.6
	1977	C	65 681	...	...	13.9	C	44 391	...	...	9.4	4.5
France	1975	C	745 065	381 804	363 261	14.1	C	560 353	291 108	269 245	10.6	3.5
	1976	C	720 395	369 439	350 956	13.6	C	557 114	...	...	10.5	3.1
	1977	C	744 830	...	...	14.0	C	535 900	...	...	10.1	3.9
German Dem. Rep.	1977	C	223 152	114 914	108 238	13.3	C	226 233	103 738	122 495	13.5	−0.2
Germany, Fed. Rep. of	1976	C	602 851	309 385	293 466	9.8	C	733 140	361 325	371 815	11.9	−2.1
	1977	C	582 348	299 736	282 612	9.5	C	704 922	347 948	356 974	11.5	−2.0
Gibraltar	1976	C	510	275	235	16.9	C	253	143	110	8.4	8.5
Greece	1977	C	143 294	...	...	15.4	C	82 895	...	...	8.9	6.5

Country or area		Natality (live-born)					General mortality					Natural increase ‰
		Code*	Number			‰	Code*	Number			‰	
			T	M	F	T		T	M	F	T	T
Holy See	1977	...	—	—	—	—	...	3	2	1	4.1	—
Hungary	1976	C	185 405	95 350	90 055	17.5	C	132 240	68 405	63 835	12.5	5.0
	1977	C	177 538	91 063	86 511	16.7	C	132 031	68 955	63 076	12.4	4.3
Iceland	1976	C	4 291	2 231	2 060	19.5	C	1 343	764	579	6.1	13.4
	1977	C	3 950	...	...	17.8	C	1 435	804	631	6.6	11.2
Ireland	1977	C	68 436	...	...	21.4	C	33 425	...	...	10.5	10.9
Isle of Man	1976	C	721	...	...	11.9	C	977	479	498	16.1	–4.2
	1977	C	672	...	...	11.0	C	1 007	...	...	16.5	–5.5
Italy	1975	C	827 852	426 160	401 692	14.8	C	554 345	...	...	9.9	4.9
	1976	C	781 570	402 428	379 142	13.9	C	546 912	...	...	9.7	4.2
	1977	C	742 546	328 077	414 469	13.1	C	542 732	...	...	9.6	3.5
Licchtenstein	1976	...	347	196	151	14.4	...	178	107	71	7.4	7.0
Luxembourg	1977	C	4 053	2 105	1 948	11.4	C	4 063	2 235	1 828	11.4	0.0
Malta	1976	C	5 696	2 945	2 751	17.3	C	2 967	1 526	1 441	9.0	8.3
	1977	C	5 793	3 057	2 736	17.8	C	2 952	1 535	1 417	9.1	8.7
Monaco	1974	...	197	...	...	8.2	...	295	...	...	12.3	–4.1
Netherlands	1976	C	177 090	91 128	85 962	12.9	C	114 454	63 963	50 491	8.3	4.6
	1977	C	173 296	88 954	84 342	12.5	C	110 093	61 260	48 833	7.9	4.6
Norway	1976	C	53 474	27 408	26 066	13.3	C	40 216	21 925	18 291	10.0	3.3
	1977	C	50 652	...	...	12.5	C	39 058	...	...	9.7	2.8
Poland	1976	C	670 140	345 608	324 532	19.5	C	304 057	163 601	140 456	8.8	10.7
	1977	C	663 000	...	...	19.1	C	313 000	...	...	9.0	10.1
Portugal	1976	C	186 712	...	...	19.2	C	101 923	...	...	10.5	8.7
Romania	1976	C	417 353	215 187	202 166	19.5	C	204 873	105 088	99 785	9.6	9.9
	1977	C	423 958	217 268	206 690	19.6	C	208 685	107 690	100 995	9.6	10.0
San Marino	1975	C	280	137	143	14.2	C	159	85	74	8.1	6.1
	1976	C	297	164	133	14.8	C	136	80	56	6.8	8.0
	1977	C	291	...	...	13.9	C	136	...	...	6.5	7.4
Spain	1975	C	669 378	346 386	322 992	19.0	C	298 192	155 471	142 721	8.5	10.5
	1976	C	662 084	340 433	321 651	18.5	C	291 573	...	...	8.1	10.4
	1977	C	661 145	351 288	309 857	18.0	C	283 452	...	...	7.7	10.3
Sweden	1977	C	96 057	...	...	11.6	C	88 202	...	...	10.7	0.9
Switzerland	1977	C	72 829	...	...	11.5	C	55 658	...	...	8.8	2.7
United Kingdom:												
England and Wales	1977	C	569 300	...	...	11.6	C	575 900	...	...	11.7	0.1
Northern Ireland	1976	C	26 361	13 542	12 819	17.1	C	17 030	8 869	8 161	11.1	6.0
	1977	C	25 437	13 154	12 283	16.5	C	16 921	8 871	8 050	11.0	5.5
Scotland	1977	C	62 126	32 153	29 973	12.0	C	62 294	31 280	31 014	12.0	0.0

Yugoslavia	1975	C	388 037	200 476	187 561	18.2	C	184 907	96 124	88 783	8.7	9.5
	1976	C	390 487	201 680	188 807	18.1	C	182 966	95 479	87 487	8.5	9.6
	1977	C	384 808	...	...	17.7	C	183 290	...	...	8.4	9.3
Oceania												
American Samoa	1976	C	1 092	584	508	35.7	C	132	90	42	4.3	31.4
Australia	1976	C	227 810	116 838	110 972	16.4	C	112 662	62 527	50 135	8.1	8.3
	1977	C	226 310	116 560	109 750	16.1	C	108 790	60 323	48 474	7.7	8.4
Christmas Island (Austr.)	1977	C	58	...	...	19.3	C	5	...	...	1.7	17.6
Cocos (Keeling) Islands	1977	C	6	...	...	13.0	C	—	—	—	0.0	13.0
Cook Islands	1976	C	458	238	220	24.9	C	107	66	41	5.8	19.1
	1977	C	505	258	247	27.4	C	172	102	70	9.3	18.1
Fiji	1976	C	16 536	8 520	8 016	28.6	C	2 571	1 581	990	4.4	24.2
French Polynesia	1972	...	4 334	...	...	35.5	...	957	...	...	7.8	27.7
Gilbert Islands	1972	U	1 131	581	550	20.0	U	362	208	154	6.4	13.6
Guam	1976	C	3 048	...	...	32.8	C	467	...	...	5.0	27.8
Nauru	1975	C	158	...	...	32.3	C	36	...	...	4.5	27.8
New Caledonia	1976	...	3 902	1 969	1 933	29.0	...	1 052	630	422	7.8	21.2
New Zealand	1977	C	54 179	27 788	26 391	17.3	C	25 961	14 317	11 644	8.3	9.0
Niue	1975	...	98	57	41	24.7	...	24	15	9	6.0	18.7
Norfolk Island	1977	C	16	...	...	8.0	C	13	...	...	6.5	1.5
Pacific Islands	1976	U	3 975	2 087	1 888	32.4	U	541	325	216	4.4	28.0
	1977	U	3 690	...	...	29.8	U	548	...	...	4.4	25.4
Papua New Guinea	1977	...	125 300	65 300	60 000	44.6	...	2 668	1 523	1 145	0.9	43.7
Samoa	1977	U	5 338	...	...	34.9	U	1 068	...	...	7.0	27.9
Solomon Islands	1969	...	5 720	...	...	35.8	...	2 060	...	...	12.9	22.9
Tokelau Islands	1972	...	49	24	25	30.6	...	9	5	4	5.6	25.0
Tonga	1976	...	1 172	...	...	13.0	...	174	...	...	1.9	11.1
Wallis and Futuna Islands	1972	...	362	...	...	42.6	...	87	...	...	10.2	32.4
Union of Soviet Socialist Republics												
USSR	1976	C	4 719 655	...	...	18.4	C	2 426 475	...	...	9.5	8.9
	1977	C	4 719 000	...	...	18.2	C	2 501 000	...	...	9.7	8.5
Byelorussian SSR	1976	C	147 900	...	...	15.7	C	82 400	...	...	8.8	6.9
	1977	C	150 200	...	...	15.9	C	85 000	...	...	9.0	6.9
Ukrainian SSR	1976	C	747 069	...	...	15.2	C	500 584	...	...	10.2	5.0

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MENTAL RETARDATION IN CHROMOSOMAL DISEASES

A. F. ZAKHAROV

Mental retardation is one of the most significant problems of human pathology facing our society. At present, this problem spreads out the frames of child psychology and psychiatry. In order to reach any progress in lowering of the incidence of mentally retarded persons and in treatment and prevention of this condition it is important to study thoroughly etiology and pathogenesis of this complex group of mental disorders gathered under the term "mental retardation". A great number of specialists among which there are embryologists, geneticists, biochemists, psychologists, pediatricians, psychiatrists and others are now engaged in appropriate activities.

In the USSR, according to a proposal made by G. A. Suchareva (1970, 1972), mental retardation (a term "oligophrenia" is used in the USSR) is considered to be a group of pathological conditions with different etiologies but having a principal factor in common: it is an anomaly of the development of the brain often combined with malformations of other body systems. Thus, this anomaly depends not only on the nature and intensity of an etiological factor but mainly on the time of exposure, i.e., the stage of ontogenesis at which the organism is damaged. Human brain is developed not only prenatally. Its ontogenically younger structures which are especially important for cognitive activity, are formed also during the first three years of postnatal life. In accordance with this supposition, clinical forms of mental retardation are divided into three groups depending on the time of the harmful factor's action, namely:

1. Mental retardation which is determined by a pathological condition of the reproductive cells of the parents. Actually this is genetically conditioned mental retardation in its numerous forms (monogenic disorders, those with a polygenic type of inheritance, chromosomal disorders).

2. Mental retardation which is caused by harmful factors acting during the intrauterine period (embryopathies and foetopathies).

3. Mental retardation which depends on damage of the brain in the perinatal period or in the first three years of life.

Among forms of mental retardation of the first group is that caused by chromosome anomalies.

Incidence of mental retardation caused by chromosome anomalies

One can judge in two ways about the incidence of mental deficiency of chromosomal origin.

The incidence can be estimated through the study of frequency of chromosome anomalies in the general population. The most reliable data were obtained by the chromosome analysis of unselected newborn children. There are several such studies, the results of four of them which were carried out on large groups of the newborn and with the use of more precise techniques of chromosome identification are presented in Table 1. As is seen there, the data obtained from the studies of the total of 42787 newborn infants are rather similar in respect to the frequencies of anomalies in each of the studies. Thus, the mean values can be regarded as reliable for the newborn as a whole.

Anomalies of sex chromosomes (mostly Klinefelter's, triple-X and Turner's syndromes) and structural changes (partial trisomies and monosomies) of autosomes in total are met with the similar frequencies: 2.2 per 1000 and 2.5 per 1000, respectively. Complete autosomal trisomies (1.5 per 1000) with the prevalence of Down's syndrome (nearly 1.3 per 1000) are observed with lower frequency. The total incidence of chromosome abnormalities is 6.3 per 1000.

It is known that not all chromosome abnormalities are accompanied by mental deficiency. It might be assumed that mental retardation accompanies probably some 50% of all the patients with chromosomal abnormalities. This estimate is certainly very approximate (to our knowledge, there are no convincing data on this point). The estimate should be hardly below 30% because autosomal trisomies and unbalanced chromosomal rearrangements are anomalies which induce mental deficiency in practically all the carriers (some 30% together, see Table 2). Carriers of balanced chromosome rearrangements are mentally subnormal in the minority of the cases, and probably some 50% of patients with sex chromosome anomalies are mentally retarded. Thus, the upper percentage

TABLE 1. *The frequency of chromosome abnormalities in unselected newborns*

Reference	Total newborns examined; country	Sex chromosome abnormalities	Trisomies autosomal	Structural rearrangements			Total
				Total	Unbalanced	Balanced	
Jacobs *et al.*, 1974	11680, Scotland	31 (0,26)	20 (0,17)	27 (0,23)	4 (0,03)	23 (0,20)	78 (0,67)
Nielsen, Sillesen, 1975	11148, Denmark	29 (0,26)	18 (0,16)	37 (0,33)	6 (0,05)	31 (0,28)	84 (0,83)
Hamerton *et al.*, 1975	13939, Canada	20 (0,14)	18 (0,13)	28 (0,20)	2 (0,01)	26 (0,19)	66 (0,46)
Kuleshov *et al.*, 1978	6000, USSR	16 (0,27)	10 (0,17)	15 (0,25)	1 (0,02)	14 (0,23)	41 (0,68)
In total	42767	96 (0,22)	66 (0,15)	107 (0,25)	13 (0,03)	94 (0,22)	269 (0,63)

Note. Numbers in parentheses are the frequency in per cent.

TABLE 2. *The relative frequency (in per cent) of chromosomal anomalies of different type among liveborns* *

Sex chromosome anomalies	Autosomal trisomies	Chromosome rearrangements	
		Unbalanced	Balanced
35,7	24,5	4,9	34,9

* Calculated on the data of table 1.

TABLE 3. *The frequency of sex chromosome anomalies in mentally retarded patients as examined by sex chromatin* (data summarized by Kuleshov)

Males		Females		Total	
Total males examined	Sex chromosome anomalies	Total females examined	Sex chromosome anomalies	Total patients examined	Sex chromosome anomalies
27464	210 (0,76)	23031	119 (0,52)	50495	329 (0,65)

Note. Numbers in parentheses are the frequency in per cent.

of mental retardation in chromosomal diseases will be hardly above 50-65% (see Table 2).

Thus, one can conclude that among 1000 newborn there will not be more than 4 and less than 2 mentally retarded children of chromosomal genesis. It is practically impossible to reveal mental retardation among newborns with certainty, and there are no data on the total incidence of this condition among the newborns. Thus, the proportion of mental deficiency of chromosomal origin among all mentally defected at birth remains undetermined.

The significant part of children with chromosomal diseases especially those having multiple congenital defects and severe mental retardation die in the first year of life. Consequently, the incidence of chromosomally caused mental deficiency among preschool and school children will be decreased. In the literature, we have found only one report on this point (Patil *et al.*, 1977). The total frequency of patients with chromosome anomalies among 4342 children 7-8 years of age was 0.48% (compared with 0.63% for the general population at birth). The frequency of sex chromosome anomalies for children of both sexes was found to be 0.23%, autosome trisomies constituted 0.04%, and structural rearrangements 0.21% (0.18% among them were balanced). We can conclude from these figures that by school age the number of children with full autosome trisomies is of 3-4 times fewer compared with those at birth, but it must be taken into account that children with Down's syndrome were excluded from the survey.

The other way to obtain data on the incidence of chromosomally conditioned mental retardation in the total population lies through the direct detection of its frequency among mentally retardates. There are a number of reports on the incidence of chromosomal anomalies among hospitalized mentally retarded individuals. The earliest surveys were conducted using sex chromatin test and therefore estimated the incidence of sex chromosome anomalies among mentally retardates. In Table 3 the data taken from 17 published reports and summarized by N. Kuleshov are presented. One can see that the total frequency of numerical sex chromosome anomalies constitutes 6,5 per 1000 unselected retardates, being higher among males (7.6 per 1000) than in females (5.2 per 1000). Klinefelter's syndrome and a 47,XXX chromosome constitution were predominant findings in these patients. The comparison with the frequency of sex chromosome anomalies in newborn population shows 3 fold increase.

Much more accurate assessment of the contribution of chromosome abnormalities to etiology of mental retardation was made through chro-

mosomal surveys of mentally retarded individuals. The largest surveys, the most recent of which were made using banding techniques, are presented and summarized in Table 4. Actually all of the surveys were made on institutionalized unselected groups of patients of different age. As can be seen from Table 4, the total incidence of patients with chromosomal abnormalities in the individual surveys is in the range 8.1% (Kondo *et al.*, 1979) to 19.7% (Grace, Ally, 1977), the mean incidence being of 11.9%. Thus, the proportion of chromosome disorders in mental subnormality hospitals is some 20 times greater than their incidence at birth (compare Tables 1 and 4). Among all chromosome abnormalities taken as 100% Down's syndrome is the predominant chromosomal disease constituting about 80% of the patients. Other autosome trisomies constitute about 4.5%, sex chromosome disorders 9% and the rest are partial monosomies and balanced structural rearrangements.

To estimate from the data presented the incidence of mental deficiency of chromosomal origin in the general population we need to know appropriate figures for mental retardation on the whole, which is 30 per 1000. If we equate the proportion of mental retardation of chromosomal nature in mental subnormality hospitals and in the general population, its incidence in the latter will be some 3 per 1000. This value is similar to that calculated above based on the incidence of chromosome abnormalities in the general population.

During the last decade when banding techniques were developed which allow exact detection of heterochromatin regions in a metaphase chromosome, structural polymorphisms of many human chromosomes were observed and their possible relation to developmental defects is now investigated. Among pathological conditions studied is mental retardation, usually of the unclassifiable type. The most relevant data published are presented in Table 5. In the majority of the studies, no significant difference was found between groups of patients with unclassifiable mental retardation and normal controls in the size, distribution and location of polymorphisms. Perhaps, in some special groups of retardates as it follows from the data of Wang and Hamerton (1979), one may expect to find some correlation between the mental retardation incidence and the frequency of extreme polymorphisms. However, the contribution of this factor to the overall incidence of mental retardation will be low taking into account the low frequency of extreme polymorphisms in the human population.

TABLE 4. *The Frequency of chromosome abnormalities in unselected mentally retarded patients*

Reference	Population examined	Total patients examined	Sex chromosome anomalies	Autosome anomalies				With anomalies in total
				Trisomy 21	Other trisomies	Deletions and rings	Balanced rearrangements	
1	2	3	4	5	6	7	8	9
Newton *et al.*, 1972	Institutionalized, 15-70 years, North England	1255	10 (0,8)	103 (8,2)	7 (0,6)	3 (0,2)	5 (0,4)	128 (10,1)
Cassiman *et al.*, 1975	Institutionalized, up to 18 years, Belgium	857	3 (0,3)	111 (12,9)	7 (0,8)	4 (0,5)	4 (0,5)	129 (15,0)
Sutherland *et al.*, 1976	Institutionalized, newborns-74 years, Australia	588	4 (0,7)	73 (12,4)	7 (1,2)	3 (0,5)	3 (0,5)	90 (15,3)
Speed *et al.*, 1976	Institutionalized and at home, Scotland	2770	31 (1,1)	250 (9,0)	11 (0,4)	5 (0,2)	0	297 (10,7)
Grace, Ally 1977	Institutionalized, 1 month-70 years, South Africa	391	15 (3,8)	45 (11,5)	0	17 (4,3)	0	77 (19,7)
Jacobs *et al.*, 1978	Institutionalized, newborns-29 years Hawaii	475	3 (0,6)	40 (8,4)	5 (1,0)	4 (0,8)	5 (1,0)	57 (12,0)
Faed *et al.*, 1979	Institutionalized, 2-73 years, Scotland	756	6 (0,8)	91 (12,0)	2 (0,3)	2 (0,3)	2 (0,3)	103 (13,6)
Kondo *et al.*, 1979	Institutionalized, 6-66 years, Japan	449	1 (0,2)	33 (7,3)	1 (0,2)	1 (0,2)	1 (0,2)	37 (8,1)
Bourgeois, Bérézech 1979	Institutionalized, France	600	11 (1,8)	32 (5,3)	2 (0,3)	2 (0,3)	3 (0,5)	50 (8,3)
TOTAL		8140	84 (1,0)	778 (9,6)	42 (0,5)	24 (0,3)	23 (0,3)	968 (11,9)

Note. Numbers in parentheses are the frequency in per cent.

TABLE 5. *Chromosome polymorphisms in mentally retarded patients*

Reference	Population and number of examined (MR/control)	Staining techniques used	Chromosomes studied	Conclusion
Mikelsaar *et al.*, 1975	Unclassifiable MR 80/208 USSR	Q	3, 4, 13-15, 21-22, Y	Increase in total frequency of brilliant bands
Podugolnikova *et al.*, 1977	Unclassifiable MR 80/80 boys USSR	Conventional	1, 9, 16, Y	No difference with controls
Funderburk *et al.*, 1978	Unclassifiable MR 1289/0 USA	Conventional	1, 9, 16, 17, 13-15, 21-22, Y	No difference with controls
Tharapel, Summitt 1978	Unclassifiable MR 200/200 USA	Conventional C	1, 9, 16, 17, 13-15, 21-22, Y	No difference with controls
Soudek, Sroka, 1979	Unclassifiable MR 100/100 Canada	Q C	1, 3, 9, 16, 13-15, 21-22, Y	Increased frequency of 9qh+
Wang, Hamerton, 1979	Down's syndrome 93/165 USA	C	1, 9, 16	Increased frequency
	Idiopathic MR 54/165 USA	C	1, 9, 16	Increased frequency
	Idiopathic MR plus multiple anomalies 48/165 USA	C	1, 9, 16	No difference with controls
	Acquired MR 69/165 USA	C	1, 9, 16	No difference with controls

PHENOTYPE-KARYOTYPE CORRELATIONS IN RESPECT TO MENTAL DEFICIENCY

Based on observations on phenotype-karyotype correlations in chromosomal diseases one may conclude that the degree of maldevelopment of brain is in parallel with severity of body malformations, and that both are in close relation to the degree of chromosome / gene imbalance. However, the problem remains unresolved and to our knowledge published reports on this special subject are scarce.

Association of sex chromosome anomalies with mental disorders is not straightforward. On the whole these anomalies result in less drastic changes in brain functioning compared with autosomal imbalance, and the degree of such changes depends on an abnormal chromosome constitution. The relevant data were reviewed by Polani (1969) and are summarized here.

Women of 45,X constitution and with partial X-monosomies are actually normal or slightly abnormal when tested on a Wechsler scale. It seems that performance IQ is significantly lower than verbal IQ and this tendency is more common in patients with typical Turner's syndrome compared with ovarian dysgenesis. Surveys indicate that the incidence of 45,X women in subnormality hospitals is slightly higher than at birth. But there is the prevalence of 45,X girls of about four to five times in schools for educationally subnormals.

Intellectual subnormality is a much more typical condition in X-chromosome polysomies 47,XXY and 47,XXX. The more extra Xs there are in karyotype the greater is mental subnormality. From the data based on the study of 17000 males in subnormality hospitals it follows that prevalence of males with Klinefelter's syndrome is four times their incidence in newborn infants for 47,XXY and five to six times for mosaics (46,XY/47,XXY). The proportion of 47,XXX females and mosaics 46,XX/47,XXX among hospitalized was 5 fold compared with that at birth. In schools for educationally subnormal 45,XXX females were two or more times more common than among the newborn.

It is pertinent to point out that there is certain correlation between X chromosome disorders and mental illness. Polani in his survey showed that sex chromatin positive males (mostly 47,XXY) among "schizophrenics" were found three times more often than their incidence at birth (1 per 166 compared with 1 per 465, respectively). The frequency of "schizophrenic" women with two sex chromatin bodies (mostly 47,XXX) was found to be 1 per 253, the prevalence being some five times the incidence at birth (1 per 1253).

Males with Klinefelter's syndrome of a 47,XYY constitution are usually not intellectually impaired to a great degree and consequently their prevalence in mental subnormality hospitals is not marked compared with 47,XXY. They are characterized by anti-social behaviour and that is why their incidence among the institutionalized violent patients is about 30 to 50 times more than in newborn males.

Autosomal disorders in survivors are observed on a large scale of maldevelopments of brain and body. Some of them are lethal or sublethal and are characterized by multiple severe congenital defects of various body systems and gross brain underdevelopment. Autosomal trisomies except trisomy 21 (mostly 8, 9, 13, and 18) are at the first place in this group. Patients with Down's syndrome (non-mosaics) are characterized by mental retardation of the moderate and severe degree. Mosaics are characterized by mild mental deficiency. Other autosomal disorders (partial trisomies and monosomies, simple and in combination) have mental retardation as a rule which is widely ranged in severity depending on a degree of gene imbalance (the size of a segment involved and its gene composition). Even some balanced structural rearrangements may be accompanied by mental deficiency. There is a suggestion that *de novo* balanced structural rearrangements are the main contributors to those associated with mental retardation (Jacobs *et al.*, 1978).

Keeping in mind that cbromosomal disorders are very variable in respect to brain maldevelopment and intellectual deficiency, some authors nevertheless attempted to outline the peculiar features of brain defects of chromosomal origin. According to M. Blumina (1970), the following features are characteristic for chromosomally determined mental retardation: *a*) combination of MR with general psychical and somatic underdevelopment and with multiple congenital abnormalities; *b*) profound underdevelopment of cognitive ability combined with the relative maintenance of primitive emotions and behaviour.

In conclusion, it should be stressed that pheno-karyotypic relationship being an extremely difficult problem to be studied in general it appears to be even more complicated when applied to a brain function. This field is practically a white spot on the map of phenotype-karyotype relations.

Mechanisms of mental retardation in chromosomal diseases

The problem of mechanisms underlying mental deficiency in chromosomal diseases is versatile. It is far from being solved, being intimately connected with our insufficient knowledge of genetic and biochemical basis

of brain normal development and functioning. Both are now the most attractive problems of current biology.

There are several ways to attack this problem. Pathoembryological and pathomorphological investigations were chronologically the first ones. Based on the numerous data obtained one may say that an intellectual defect in the majority of chromosomal diseases (perhaps, except sex chromosome disorders) is the manifestation of the anomalous development, immaturity of the brain. Such microscopically detected abnormalities as delayed myelination of white matter, immature differentiation of ganglion cells, and embryonic cell piles are common findings, for example, in Down's syndrome. The pathologic changes at the cellular level should be regarded as primary ones directly connected with chromosome imbalance. According to a series of studies of cellular phenotype in autosomal trisomies and monosomy performed in the Institute of Medical Genetics in Moscow, in which cultured cells of chromosomally abnormal abortuses and liveborns were used, chromosome abnormality may change primary morphogenetic cell reactions (such as cellular reproduction, migration, differentiation) disturbing interactions between cells and contributing in this way to the disturbances of histogenesis and morphogenesis at the organism level.

It is well known that brain formation is a very prolonged process even continuing for the first three years of postnatal life. There exists a wide gap between terms of maturation of its different parts. Thus, morphoembryological basis of brain maldevelopment should be varied in dependence on the severity of chromosome imbalance, which in its turn, conditions the time and intensity of harmful effects during ontogenesis. Autosomal disorders are mostly embryopathies and pathologic effects are developed when histogenesis is still in progress. These effects are mostly lethal inducing embryonic and foetal death. Survivors will have multiple congenital defects as the result of underdevelopment. Mental deficiency in these cases is the result of hypoplasia of the brain. Gene imbalance in chromosomal diseases of a slight degree (sex chromosome anomalies, balanced structural rearrangements) probably does not damage embryonic development but contributes to brain impairment in later stages of foetal life, and the phenotypic effects will be less expressed in general, with slight subnormality in respect to brain function.

The other approach to understand pathogenesis of mental deficiency in chromosomal disorders is to study what happens with genetic information in the cell having gene disbalance. It is this event that is the first link in a chain of pathogenesis of a chromosomal disease. According to Polani

(1969), one should distinguish three types of genetic effects of chromosome imbalance: specific, semi-specific and non-specific.

Specific effect is due to the change in the dose of structural genes which are located in the chromosome involved. Since the discovery of the dosage effect for gene SOD-I in trisomy 21 in 1974, some 20 other genes were shown to be expressed in this manner. It might be that some phenotypic features could be attributed to such simple mode of gene information disturbance. However, in real situations enzymatic activity may be non-proportional to the number of corresponding alleles. Besides, enzyme and other protein synthesis and their metabolism are a carefully regulated and adjusted process, so that a simple change in the quantity of one gene product will lead to at least quantitative disturbance in metabolism of others. We know how easily this discorrelation occurs from the data on the blockade of one enzyme production vs. catabolism in monogenic enzymopathies. We know also from studies of enzymes activity in chromosomally unbalanced cells that the shift in the level of activity concerns many enzymes which are coded by genes located in chromosomes non-involved into a given rearrangement. One should not forget either that in what we call chromosomal diseases many hundreds and thousands of genes are involved in structural dishalance. Thus, the final picture of the disturbance of metabolism of the cell caused by "specific" genes effect appears to be extremely complicated.

Semi-specific effects may be attributed to the change in the dose of those genes that are multiple and serve some key steps of cellular metabolism. Among them are ribosomal genes and those coding histones and tRNA production. We cannot disregard this effect, for example, when acrocentric chromosomes are changed in the number or structure.

Non-specific effects are connected with imbalance of heterochromatin content in a cell, which is present in every chromosome. The genetic role of heterochromatin in concrete terms of gene action remains obscure although nowadays the progress in molecular genetics promises to contribute to elucidation of its genetic significance. Nevertheless, a bulk of various observations made with different species gives many empirically found indications to its important role both in the activities of a cell and in the evolution of a species. It is proposed that at the cellular level heterochromatin affects the pattern and speed of cell division and growth. If this is so, this effect is particularly relevant to "unspecific" disturbance of cell propagation, differentiation and movement which is observed in all chromosomal diseases and contributes to the distortion of morphogenesis irrespective of specificity of a chromosome involved. How heterochromatin

works in this direction is now known. Perhaps, as was suggested long ago, heterochromatin contains many genes with similar, small and supplementary effects contributing to a given quantitative character.

It has also been shown that some chromosomal regions appearing heterochromatic in postnatal life are transcriptionally active during embryonic and/or foetal development. In any case, deviation in heterochromatin content should be taken into account when genetic mechanisms of malformation are considered.

Concerning brain maldevelopment, heterochromatin imbalance is considered an important causative factor at least in sex chromosome diseases. According to Hamerton, both stature and psychosocial development abnormalities observed in these cases may be due to variation in content of sex-chromosome heterochromatin. Both these characters are quantitative and closely connected with cell propagation, growth and differentiation, and therefore, might be expected to be controlled through heterochromatin.

Taken together, morphoembryological and genetic data indicate that mental deficiency as well as other malformations in chromosomal diseases are due mainly to those pathogenetic factors which are very common in different chromosome abnormalities and therefore may be called «unspecific". Such an interpretation is consistent with clinical manifestation of chromosome abnormalities which is very similar in different diseases so that chromosomal syndromes are delineated rather by relatively specific combinations of defects than the presence of unique features.

However, it would be a mistake to reject the existence of specific genetic and phenotypic components in a given chromosomal disease. The more we learn of the relations between types of changes of a given chromosome and corresponding phenotypic manifestations, the more evident is dependence of a specific pbenotypic feature on the gain or loss of specific chromosomal segment. The specific Down's phenotype is found only when band 21q22I is trisomic, in cri-du-chat syndrome the midportion of the 5pI5 band seems to be a critical one, and in Edward's syndrome the most characteristic features seem to be connected with band I8qII. Another evidence of this statement comes with the description of alternative phenotypes (types and contratypes) wbich correspond to a trisomic or monosomic state of a given chromosomal segment.

As to mental deficiency, it is not a simple task to discriminate specific and unspecific components of the relevant genetic contribution to its development. Biochemical approach promises to be the most precise and profitable way to advance in this field. One can completely agree with

prof. J. Lejeune (1977) that human intelligence "... needs the concourse of an enormous array of morphological and chemical functions highly integrated", and in this respect hundreds of different proteins including enzymes are engaged in normal brain activities, but it does not mean that there exist many special "intelligence" genes.

Biochemical approach can be realized through: *a*) gene mapping and a study of the gene dosage effect at the cellular level; *b*) biochemical investigations at the organism level; *c*) pharmacological approach at the organism level. This scheme of investigations was shown to be very fruitful by prof. J. Lejeune in his studies on Down's syndrome. Looking at the author's even simplified scheme of metabolisms involved in adrenergic and cholinergic mediators' machinery and following his analysis of clinical features and biochemical (gene) disturbances common and different for trisomy 21, trisomy 12p, and homocystinuria, one should completely agree with the author's statements: *a*) clinical symptoms, gene mapping and biochemical disturbances are to be correlated to understand the mechanism of mental deficiency; *b*) the mechanism at the final stage of our understanding can be expressed in concrete biochemical terms.

Incidence of mental retardation

Estimates of incidence of mental retardation in populations depend very much on approaches to definition and classification of this complex group of diseases with mental deficiency as a main symptom, and consequently to criteria to be used to assess this condition. The corresponding principles used in the USSR are not similar to those in the USA and other Western countries. In the USA mental retardation is defined as a condition of a person characterized by intellectual deficiency which impairs his adaptation and successful competition in the community. Accordingly, mentally retardates are detected by the psychological criteria (IQ scores), and an individual is labeled as being mentally retarded if he performs two standard deviations below the mean on a standardized psychologic test. Based on these IQ scores, mental retardation is found in some 3% of the general population in the USA. Intelligence tests are of great value in assessing the level of mental deficiency. But they were criticized much because this approach ignores clinical and sociocultural aspects. The corresponding recommendations were made for use in International Classification of Diseases at the fifth Seminar in WHO.

The definition of mental retardation in the Soviet Union is based mostly on clinical principles, taking into account the following information

on each individual examined: *a*) etiological or pathogenically associated factors of biological or organic nature; *b*) associated neuro-psychiatric disorders; *c*) associated psycho-social factors. Certainly, the degree of mental deficiency is taken into consideration but only as a guide in the appropriate analysis made by psychiatrists.

In accordance with these principles those forms of intellectual deficiency that are due to incorrect child rearing, a slow rate of general development and to asthenia induced hy somatic causes are not included in the category "mental retardation" (oligophrenia). Moreover, as it was stated above in this haper, according to Prof. G. Sukhareva's proposal mental retardation is a group of diseases which is characterized by: *a*) underdevelopment of the brain as a morphophysiological basis of the disease; *b*) nonprogress of the condition which is completely formed prenatally or during the first three years of postnatal life. Thus, intellectual defect caused by damage to brain that has already been formed is not included in mental retardation either.

The difference in definition should be taken into account considering the difference hetween MR frequency estimates in Western countries and the USSR. The data on MR incidence in the latter obtained on the basis of the above-mentioned criteria can be illustrated with a typical survey made by Goldovskaya and Timofeeva (1970) in four large cities of the Russian Soviet Socialist Federative Republic. The incidence of mental retardation was as follows: Kemerovo — 4.89 per 1000, Tula — 4.32 per 1000, Sverdlovsk — 4.72 per 1000, Saratov — 2.38 per 1000. The relative frequencies of MR of different degree in the average for all four cities was the following: the mild category 80.8%, the moderate one 15.9%, severe MR 3,8%. These figures are consistent with those observed in other countries.

Consistent with data published in Western countries are the results on the time of recognition of mental retardates obtained in the same work. At the age of 0 to 2 years only 15.5% of the retardates are registered, and 49.6% of children with MR are first registered by psychoneurologists at the age of 7 to 10 years when their intellectual competence is first challenged at school. In accordance with other published data there is also a drop in the frequency of identified cases after adolescence: 63.5% of all the retardates were up to 19 years old and 6.8% only were 40 and older.

The low overall MR incidence observed in the study in question is typical for other similar surveys. The explanation of the difference with estimates in the USA seems to be simple: underestimation of the real

frequencies using the above-mentioned clinical criteria, as well as overestimation when intelligence test only is used. The validity of this explanation follows from another study. Using a modified test on a Wechsler scale in the study of children of 7-15 years of age the frequency of MR was found to be 29 per 1000 (27 per 1000 being mildly retardates). Thus we may conclude that the overall incidence of MR as well as its distribution by degree of deficiency seem to be very similar in different developed countries.

Specialized institutions for care, education, and training of mental retardates

In the USSR the task of prevention of mental retardation is accomplished through the state system of institutions and activities to safeguard the health of mothers and children. We shall not discuss this system but outline what we call the differential network of preschool and school institutions for mentally retarded children. It is a part of the system of institutions for handicapped children in general, including specialized kindergartens and schools for children with impaired sight, hearing, speech, etc.

Primary examination of a suspected retarded child is carried out at a district out-patient department by a pediatrician (often a pediatric neurologist) in cooperation with a pediatric psychiatrist. When diagnosis is confirmed the child will be registered in a special neuro-psychiatric dispensary. The final diagnosis and decision as to where to take care of the child is made by a district team of specialists that includes besides a pediatrician and psychiatrist a psychologist and educational worker. In most complicated cases referral to a major (at the level of city) diagnostic and/or treatment center is practiced.

The network of institutions for mentally retarded children is governed by three Ministries: of Health, Education, and Welfare.

Mental retardates at the age of up to 4 years are under the auspices of the Ministry of Health. There are special kindergartens of two types for children with MR associated with organic damage of the central nervous system: *a*) with permanent institutionalization and *b*) those with the possibility for parents to take their child home for week-ends. In spite of continuing progress in the expansion of the network of such preschool institutions, there is a shortage of them, and further organizational efforts should be made. Meanwhile special separate groups for mild uncomplicated retardates are organized in regular kindergartens. There are also under

medical control special preschools for educable mentally retarded children with organic damage at the age of 4 to 8 years.

By the time of school education children from the abovementioned institutions are transferred to institutions that are under the control of the Ministry of Education. The following network of institutions for educable mental retardates is functioning: *a*) special preschools for educable not severely affected children; *b*) auxiliary schools where MR children capable to learn are educated; *c*) special institutions ("child houses") for mentally retarded children of school age who have organic defects of CNS.

Under the government of the Ministry of Welfare is a set of institutions for those mentally retarded individuals who are severely affected and not-educable in auxiliary schools and cannot be trained to self-care activities. These institutions are subdivided according to the age of the invalids: *a*) for children of preschool age; *b*) for school-age persons (8-18 years), *c*) for adults.

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EARLY TREATMENT AND TRAINING FOR THE CHILD WITH DOWN'S SYNDROME

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Down's Syndrome is the commonest single condition in mental subnormality, comprising between 1 in 600 and 1 in 700 births. It has long been regarded as one of the most intractable conditions to treat, and any method that can reduce appreciably the degree of mental subnormality associated with the condition would be likely to have a considerable social impact. It is the aim of this introductory paper to give a brief account of work that appears to have achieved this end to a small but significant degree.

My own interest in and acquaintance with the condition has a long and complex history which cannot be fully set out here. Briefly, I first encountered it in infancy in the 1930's, when two relatives suffered from it. Later, I spent 22 years as a teacher of educationally backward children in Secondary Schools, and this led indirectly to a renewed interest in the condition. I was for ten years the Head of one of the largest Departments of its kind in Britain, and was concerned with the entire academic education of a large number of backward children with Intelligence Quotients ranging usually from around 50 to around 120, the causes of educational backwardness being very diverse.

My early research in education had indicated a striking correlation between social class and school class in British Secondary Schools, and this led to a deeper study of the history of many of my pupils. I was rapidly convinced that their early history of deprivation of various kinds could well account for the limited intelligence of many of my pupils, as by following their history back to birth, I discovered that professional observers had in many cases rated them as infants as normal and even bright at that point. This led to a general interest in the century-old

controversy concerning the relative contribution of heredity and environment to the variance of test intelligence. Most of the classic studies (some of them now discredited somewhat by the discovery of the falsity of much of Sir Cyril Burt's data) had been carried out on identical twins brought up in different environments. However, after some years of study of a variety of mental and physical handicaps, my attention was caught by the announcement in 1959 by Lejeune, Gautier and Turpin of the discovery of the supernumery chromosome 21 in Down's Syndrome, and at once conceived the idea that, though this condition was not as a rule hereditary, it was the most serious genetic anomaly then known, and that it could thus be a possible test case in the above mentioned controversy, should it prove that environmental manipulation could bring about any significant improvement in the Down's child's intelligence. I, therefore, studied the condition in some detail, and was kindly encouraged in my studies by the late Professor Penrose, who was good enough to correspond with me and correct various erroneous ideas.

As such children did not, however, fall within my orbit, and I felt that in any event any intervention would have to take place very early in life, my vague theories might very well have come to nothing. My reading had, however, suggested that parents of such children, given the generally very gloomy and sometimes brutal prognosis of their doctors, might very well do nothing for their child in the early years of life, which, as Gesell and Amatruda wrote in 1949, are crucial to the development of handicapped children. It appeared that they either died very early in life or were commonly left for long periods immobile in their cots by parents stricken by their tragedy, and often with unwarranted feelings of guilt towards their child. Centerwall and Centerwall (1960) had indicated that there was a significant and lasting advantage to children brought up in their own homes for some years before admission to an institution compared with those who were admitted early, and it seemed that even if the home were relatively unstimulating, it was better than the very unstimulating environment of a large and impersonal institution. Benda (1949; 1960) had carried out many pathological studies which indicated that the brain in Down's Syndrome was severely underdeveloped and unmyelinated rather than actually damaged, and Kirman (1953) had suggested that the brain abnormality was diffuse and might possibly be reversible at some future time.

In 1963 I married and acquired two stepsons, one a brain-damaged

boy, who did not subsequently speak until he was 7½ years old. Largely through the efforts of my wife, those of the Birmingham Schools Psychological Service and his excellent Special School which he attended until he was transferred to a normal Secondary School at the age of 11, he is now a perfectly normal young man, who lives a normal and independent life, and has been in steady employment for the past four years. At the time, however, he presented many of the characteristic behavioural problems of the mentally handicapped. Two years later, my younger daughter was born with Down's Syndrome.

I recognised her condition at once, but did not communicate the news to my wife for a day, until the condition had been confirmed by the paediatrician. She, however, though unfamiliar with the condition, had already recognised that our child was not a normal baby, and had read the medical note "mongoloid facies" at the foot of her bed. Unlike many parents she accepted her baby at once, while I spent a worried night wondering how to break the possibly crushing news to her that we had another handicapped child. Though I had grown up without the customary prejudices against the "mongol" child, I found my own difficult to accept under these circumstances until after much reflection and not a little prayer for the strength to face the new problem, I decided that as my educational career and my earlier studies had left me better prepared than most parents for such an event, I would devote myself to her service and to that of all others like her, a vow that I have since maintained.

My daughter was a very unpromising case, more severely hypotonic than almost any of the thousands of such children with whom I have been subsequently concerned, totally inert with the characteristic mongoloid facies and vacant expression. Her spinal reflexes which I tested extensively gave no cause for optimism either, as they were totally negative as in the case of the Landau reflex, or doubtful, partial or unilateral in the case of the Moro and Crossed-Extension reflex. The only brisk response was to do the plantar scratch test. From Benda's description of the brain in this condition, I realised that it would probably be very unresponsive to stimuli and would require a very high level of stimulation if it were to have any chance of development. I had by a happy chance read the classic, but unwarrantedly forgotten work of Edouard Seguin, the great pupil of Jean Itard, at University in 1949, and must acknowledge a debt to this great pioneer, whose work has had, through his successors, such a large effect on infant and child education in the Western World.

Though I did not adopt his methods as such, I was influenced by his very interesting principles. As at first my child responded to nothing apparently, apart from her scratch reflex, I began work here by stimulating the reflex recoil while restraining her limb with my other hand in the hope that this would strengthen the afferent signals through her tendon stretch sensors and muscle spindles. I then extended this approach over a period to all her muscles and tendons by compressing the latter against her joints to place them under a tension which would otherwise be absent in her current state of hypotonia, while exercising the limbs gently against the joints. Detailed records of observations were kept and this initiative appeared to be having some effect, though very slowly. Meanwhile we arranged to assail all her senses, visual, auditory, tactile, kinaesthetic and proprioceptive with a vigorous barrage of stimulation. Space precludes a full account of this work, which has heen generally described in Brinkworth (1966, 1968, and 1973, 1975) but stimuli included vivid and rhythmic music, toys in hrilliant colours, and, when she was still in her cot various mobiles were suspended in her line of view, and sets of plastic rattles were strung across her cot and their arrangement changed every time we passed the cot to provide a constantly changing visual environment.

As her hands remained practically inert, we then took a series of measures to improve the situation. I realised that as such hypotonic children are generally left lying on their backs with hands at their sides, and as they do not raise their hands to the midline as do normal infants so that they are within their field of view, they would probably be unable to integrate the impulses from vision and touch. As a result, the poor stereognosis and manual clumsiness observed in Down's children by O'Connor and Hermelin would be adequately explained. I therefore raised her hands passively to the midline and proceeded daily with a series of hand and finger exercises. At first, since her hands did not grasp voluntarily, I concentrated on making her aware of her fingers hy intertwining them together to send a volley of signals to the brain, and having observed that unlike those of a normal baby, my daughter's hands closed with all four figures together as though she were unaware that they were separate digits, I ran a pencil firmly across the back of her fingers, in the manner of a child running a stick along a fence, with the object again of sending a rapid sequential volley of strong signals from her separate fingers to her brain. This exercise had a positive reward

very rapidly since, for the first time in my records, I observed a new expression on her usually blank face, a slight frown, a fixed gaze, and an evident expression of curiosity. For the first time as I held her hands in her field of view, she parted her fingers spontaneously and regarded her finger movements with evident interest.

On the gross motor side, we were simultaneously exercising her with the aim of giving her head control, this being very poor owing to her hypotonia. We removed her from the cot as often as possible and exercised her either on the floor or on a towel set on a table where she was bathed and changed. I acted on the idea that if I placed her in a sufficiently uncomfortable position, she would have an incentive to change her position. One of the earliest methods was to lay her face down on the carpet, which constricted her breathing, and led at first to generalised body movements, and tben to the appearance of tension in the muscles at the back of her neck. Gradually she began to raise her head, and we rewarded her by showing her a brightly coloured toy which made an attractive sound at a point where she had to raise her head and her eyes to see it well. Then we turned her on her back and lifted her by the shoulders so that her head hung limply back and was just supported by the ground. Care was taken at first not to lift her head as in Down's Syndrome the atlas joint is rather insecure and it would be easy to dislocate the neck. Again, this position restricted her breathing and led her to attempt to relieve her discomfort by lifting her head slightly herself. Through these exercises, her head control steadily progressed, and we moved forward to lap exercises, where she was held as before with her head hanging back, then was raised slowly until her head reached a point of balance, at which point again we attracted her attention with a coloured toy, and she had to make a minimal effort to pull her head up and forward past the balance point. This progressed over the months to exercises where she was held by the upper arms and pulled up and allowed to lie back alternately in a kind of "rowing" exercise.

By this time her hypotonia was much diminished, and at two months we transferred her from her cot, where she had a limited visual environment, to a Baby-Relax chair where she was supported a little above tbe horizontal. This had three major advantages: that she was removed from the social isolation of her cot into the centre of family society, could see things at various distances and could, for the first time, take an interest in moving persons. The chair also had the great advantage of a

tray which supported her still rather weak arms with her hands in her line of sight, so that manual exercises could be carried out more effectively. In the course of the first year I concentrated much attention to the attainment of precision movement with her hands, as the hands, and in particular the finger and thumb, are very largely represented in the sensory and motor areas of the brain. In parenthesis here, I should say that I was aware of the finding by Benda, later confirmed by Cowie, that in Down's Syndrome the cerebellum is very small even in relation to the rather small brain to which it is attached, and I felt that since this is closely linked with physical activity, it would benefit in its development from as much gross and fine motor activity as could be induced by my various methods. Later I was to find from Dobbing that the human cerebellum develops entirely in the first 10 months of life, which adds strength to the view that the Down's child's limited early motor activity may be both caused and reflected in the poor development of the cerebellum, and that deficiency here was one of the causes, at least, of its hypotonia. It has become very clear to me, from my results with "control" children treated only after the end of the first year, as the figures will show, that while the "controls" do improve slightly, far more dramatic and lasting effects demand a start on the work as near to birth as possible. This finding has not, I believe, been previously reported.

It is to be noted in this context that in their recent study, Piper and Pless (1980) in an excellent double-blind study, found no significant improvement in developmental Quotients in Down's children treated by an intervention method which has something in common with mine. The difference, I feel, lay in the fact that they specified their subjects as being under 24 months of age, with an average of 9 months. I would comment that the experiment began too late for the best results, as at least half of the children would have begun at the age when they would have been only partly treated "controls" in my own study, and the results reported do not therefore surprise me greatly.

Our work continued on all fronts, with such exercises as were necessary to teach our child to roll over, first from side to back, then from front to back or the converse, and with much manual training. The latter progressed from a very simple start to much more complex activity. At an early stage, before my daughter could grasp voluntarily, her tactile senses were stimulated by placing objects of differing size, shape and texture in her two hands and the hands were clasped passively round them.

Such widely differing objects as a piece of rough brick and a piece of silk were placed in her separate hands simultaneously, as I reasoned that the human brain is an expert comparator above all, and such differing signals were bound to stimulate its activity via the tactile senses.

Next, a ring on a string was placed in her hands, each in turn, and was then pulled gently, as she had now begun to have a reflex grasp. As her hand tightened on the ring, I drew it and her hand gently out to arm's length with the object of teaching her ideas of distance and space, and of teaching her gradually to reach out and grasp objects at a distance. This exercise too proved very effective and she soon learned to reach and grasp. In her cot too we had from an early point suspended two chains of plastic rattles down each side of the cot to touch her outstretched hands. The object of this was at first to reward even the slightest spasmodic movement of the hands with an interesting sound. Now, she began to grasp at the chains and pull on them to produce the sound voluntarily. I had the doubtful advantage here of being a life-long insomniac, and found that though my child was at first very inert during the day, she was relatively more active in the night. My records show a fascinating progression from accidental and sporadic rattling to more and more active and deliberate play with these rattle chains.

As the year progressed and her head control rapidly improved, we were able to raise her progressively in her special chair from near horizontal to a full sitting position, and she played more and more at reaching, grasping and handling a variety of ohjects. Towards her ninth month, we were able to suspend her in a Baby-Bouncer so that she stood on her feet, and could turn round to watch what was going on in the house, as the Bouncer was hung from the lintel of a door. We added strings of objects to hang from the cross bar of the Bouncer, objects such as small bells and rattles so that she would reach out for these and as her centre of gravity moved, she would be able to practice the sense of balance. To encourage her to move her weight from one foot to the other, we placed a stiff-haired coconut mat under her feet, on the reasonable assumption that though Down's children are less sensitive than ourselves, it would make us uncomfortable to stand barefoot on such a mat for any length of time, and even her weaker tactile senses might induce her to make dancing movements, as indeed they did.

By one year, her manual precision was much improved, and we proceeded to such exercises as getting ber to push wooden rods through

orifices. At first these were as large as the gap between the spokes of the wheels of her perambulator, then gradually the task was stiffened until she could neatly pass a knitting needle through the small holes in a sink-tidy (a small strainer) used in a kitchen sink to trap solid objects and tea-leaves. Knowing too that our children have some difficulty in the precision grip of finger and thumb as their thumb is low set, we spent much time on teaching her this art. At first, we offered brightly coloured rods horizontally into the notch between finger and thumb, which forced these to close mechanically on the object. Then we moved forward to the use of an idea adapted from the method British troops used during World War II to catch monkeys in the Far East. They used a jam tin nailed to a tree with a small piece of food inside it. The tin was of just such a size as to admit the open fingers of the monkey but too small to release its clenched fist. As monkeys refuse to let the bait go, they are therefore trapped. I adapted this idea by constructing a cylinder of transparent perspex mounted with strong glue on a board which we could hold and placed a very small sweet or toy inside. My daughter reacted just as the monkeys did, but, having found that her hand became trapped, she showed the mental superiority of Man by relaxing her grip so that her hand was released, but came out with all four fingers together with her thumb. Often by this means her outstretched fingers succeeded in escaping with the bait, and her finger and thumb grip steadily improved. At just under one year, we began seriously to teach her to feed herself with a spoon. At first, we merely encouraged her to hold and play with it, then we held her hand guided the spoon into the food, then up to her mouth, releasing our grasp when her hand was half an inch from her lips. At first, she commonly dropped the food, but steadily progressed until she could get the spoon into her mouth and was automatically rewarded by the food. We continued this work by steadily moving the spoon further and further from her mouth before releasing it, so that she had to move it further and further to obtain her reward, until she could complete the movement of the spoon from the plate to her mouth independently. By the age of thirteen months she could feed herself well with a spoon.

By the age of one year, my daughter had evidently made immense progress from a beginning so unpromising that the French Consul in Birmingham (with whom her birth was also registered, as my wife is French and my daughter has dual nationality) had commented "Quel dom-

mage. Elle ne sera jamais qu'un légume.", a view our medical advisers did not attempt to dispel. When tested on the Griffiths Scales, first by myself and then independently by Dr. Kirman and Elspeth Robertson at St. Mary's Hospital, Carshalton, she achieved a developmental Quotient of 83-85, with good scores on all scales except for language.

While, as will be described, the work continued systematically throughout her pre-school years, it already appeared to me that we had made something of a break-through, and I reverted to my original thought of 1959 that our children would throw some light on the relative importance of heredity and environment to the development of intelligence. I, therefore, applied for an advanced course in Child Psychology at the University of Birmingham with the partial object of carrying out an experimental test on other Down's Syndrome children to see if my methods were only applicable to my own child or whether they would prove of general application in this condition. With the kind co-operation of the Deputy Medical Officer of Health for Birmingham and of five paediatricians, I was put into contact with the parents of five Down's children born within a few months in Birmingham. I visited these families once a week and gave detailed instructions to their parents, demonstrating each point, and setting out in writing the necessary steps to be taken in each succeeding week. Each visit lasted for an average of four hours. When the children were six months of age, and were clearly making progress, I carried out a test against eight Control children born fractionally before or fractionally after the experimental group. Results were very positively in favour of the treated cases, and the early results are here set out.

Experimental Group (Three girls, two boys)
Griffiths test scores (Quotients)

	Locomotor.	Personal/ Social	Hearing/ Speech	Eye/ Hand	Performance.	Full-Scale D.Q.
Mean	85.5	104.6	99.9	113.2	126.8	101.8
S.D.	14.98	15.64	22.56	19.32	25.85	18.45
Controls (4 boys, 4 girls)						
Mean	70.9	76.0	69.7	81.4	77.8	75.0
S.D.	26.78	20.78	8.43	8.41	19.9	17.21

These results were processed by Fisher's statistical method for small samples, and gave the following results:

	Locomotor.	Personal/ Social	Hearing/ Speech	Eye/ Hand	Performance.	Full-Scale D.Q.
Value of T	1.01	2.381	2.99	2.705	3.307	2.361
P+	Over 0.2 (not significant)	under 0.05	under 0.02	under 0.05	under 0.01	under 0.05

As will be seen, all results showed a significant advantage to the experimental group with the exception of the Locomotor Scale. The latter result is understandable as I have placed more emphasis on fine motor training than on gross motor activity up to this point. While I was necessarily cautious in my dissertation (Brinkworth, 1967) in drawing too large a conclusion from such a small sample, the results were encouraging and remained significant even when I applied a correction factor for the greater age of the controls since as Loeffler and Smith (1964) in Penrose and Smith (1966) and other workers had observed, quotients in Down's Syndrome steadily fall in the early years of life. Comparison was also made with the most advanced home-based cases from Centerwall and Centerwall (1960) and results remained significant at below the 0.05 level of confidence.

Clarke in Clarke and Clarke (1973) discussed my paper and criticised this early study on the valid grounds that first the experimenter was also the assessor (though I had no alternative at this time) and also because he did not agree that the advantage would be lasting, after only a six-month period of training. He did not know, however, that I intended to follow these children at least up to school age, and to continue the treatment as my own system for my daughter developed. This I have since done, as far as possible. It should be noted that of the five original experimental children, one was the child of parents who were themselves of limited intelligence. The mother carried out the work very reluctantly and perfunctorily, and abandoned it at six months, despite encouragement to continue, while in one of the other cases, the parents, who had high social ambitions for their other children and had a very active social life of their own, discontinued the work at 18 months against my advice while grossly over-indulging their child, again contrary to my advice.

These two children are the only ones who have since had to attend schools for the Severely Subnormal, one of them, the latter, having become a rather unpleasant and naughty child, as well as having a quotient of only 47 at school age, when the parents returned to me for help, unfortunately much too late for satisfactory results, though some improvement has been obtained. The three others all attend schools for the Mildly Subnormal and have I.Q's above 60. Of the controls only one, whose parents started the work at 10½ months, has continued the work up to to-day, and theirs is the only child in the control group who has attended a school for the Mildly Subnormal and has an I.Q. also of 60. One of the control children has also since died.

As my own work at school was very demanding, I had not at first contemplated taking on further cases, but hoped to follow the original sample to school age or up to age 18. However, the paediatricians who had been impressed by the early results continued to refer children to me and the work became better known when with Dr. Collins I wrote a small book (Brinkworth and Collins, 1968) setting out the work as it had developed up to then. By 1968, 130 children had been referred to me and the work had become exceedingly heavy, as I worked alone and had to visit parents over a radius of 100 miles in evenings, weekends and holidays. This excessive work load damaged my health and put me out of action altogether for four months in 1968, with vertigo and hysterical paralysis.

My wife and I then had an extremely difficult moral decision to make. Should we concentrate all our attention, in such time as was available, on our own child to make her perhaps the brightest Down's child ever, or should we devote our time to extending the advantages our daughter had had to hundreds, perhaps thousands of other children, in the knowledge that tbe work would probably make our own family life very difficult and restrict the time available for the work with our own child? After much discussion, we made the latter choice, and as it was clearly impossible for me to work a 90-hour week in visiting parents over such a large area, I sought a Centre to which parents could bring their children to see me, and I set out our recommendations in great detail on paper (Brinkworth 1967-73). Thus I began to use the Quinborne Community Centre with the kind permission of the Warden, Mrs. Laurie Cordukes, for interviews and testing of the children. Six months later, a Steering Committee was formed from interested parents, psychologists

and educationists, with the objective of founding a new Association. In 1970, the Association, now Down's Children's Association, was set up and has continued to thrive, though our membership fee is very small, and we could not continue without generous voluntary donations from various sources. We now have eight branches in England and Scotland and a number of overseas affiliates. We have since been responsible for the treatment of some 3,000 children from most countries between Iceland and Australia in this hemisphere and from Canada to Chile in the Americas.

Research has been continuous and despite many difficulties resulting from my very heavy work of correspondence, testing and home visits, when the latter have been requested by doctors and paediatricians, I have continued to build up a complete scheme of compensatory education for my own child. In due course all successful interventions have been committed to paper, and have been made available to our members.

In outlining roughly some of the work done on the psychomotor side with our children, I have not set out in detail the elaborate methods of language training which we also use. This began by our naming every object that our children touched and showed interest in, so that they could, before they could speak, indicate by pointing or eye-pointing any named object. This work gradually progressed to very realistic pictures (to recognise a picture is a very large step forward in a child's development), and from there to pre-reading and pre-writing, where I used my existing skills as a veteran teacher of reading and writing to backward children. This I have developed to a fine art, and though room here will not allow for a full description, I can say that we began such work with my daughter as early as two years, and she could already recognise and read many words from flash cards before she could speak fluently herself voluntarily. Most textbooks say that Down's children cannot read or write, and cannot grasp arithmetic. I have not found this to be true with proper preparation, as many of our treated children can do both quite adequately. There is a very large bonus to be reaped from teaching children to read, for their speech develops very slowly and through reading, both their vocabulary can be vastly extended, and as expert mimics, they adopt whole phrases learned from books as part of their own speech, and the whole process of thought is thereby greatly improved. Moreover, even in those children who will never learn to read with full comprehension, owing to low intelligence, the practice of reading training helps them too to develop spoken language and to understand it.

A further important factor in our treatment, which really requires another paper to describe fully, is the dietary treatment we employ. From the start, I was influenced by the work of Himwich, Fazekas and Nesin (1940) on oxygen and carbohydrate metaholism in the brain of the Down's child and by the work of Benda on the liver, from which I conceived the idea that the inefficient liver of the Down's infant could not readily metabolise complex carbohydrates, but would become infiltrated with fat, and allow fat to be deposited elsewhere in the body. To avoid the obesity so common in Down's Syndrome, I removed all carbohydrates from our children's diet, except for glucose, which is the simplest form and the most easily used in the body, leaving only excretable residues of CO_2 and water, while providing the child with adequate energy. This method appears to have been successful in most cases, as most of our treated children are slim and active, though my own daughter at puberty is a solid stocky child herself, having put on weight in recent years, as she has eaten a more and more normal diet. Much of her weight, however, is made up of her powerful muscles. Paradoxically, in view of her feebleness as a baby, she is now formidably strong, and could lift me off the ground even at the age of six.

From an early age, too, she has been consistently on vitamin supplements from Vitamin A to D, and for the past decade vitamin E (alpha tocopherol). Indications for this vitamin treatment have come from many sources, which cannot be cited here in the space available though I should in particular mention the work of Coleman (1973) as providing some support for the belief that Vitamin B6 is of value in forming part of the metabolic chain between tryptophane and serotonin, a neurotransmitter which is in short supply in the Down's Infant, and the work of Saxl et al. (1968) on electron microscopic examination of biopsy specimens of the intestinal mucosa in Down's Syndrome which suggested to me that transport of the oil-bound vitamins in particular would probably be poor. Briefly, I have used Vitamin A to keep our children's skins, mucous membranes and sight in good order, Vitamin D to help raise their low calcium levels, the B group for general improvement of their nervous systems, and Vitamin E to combat, as an antioxydant, the superoxydation which is found in Down's syndrome. In the latter respect, I was first interested in this through study of work by Mason, Dam and Granados (1946) on Vitamin E deficiency in rats, who showed certain anatomical abnormalities resembling those seen in Down's Syndrome, and hy the work of Pryor (1970) which

showed premature ageing in mice deprived of Vitamin E. The latter showed that the cells suffered from the damaging effects of free radicals, and in view of the common phenomenon of premature ageing and Alzheimer's disease in Down's patients, I felt that Vitamin E supplementation would be vital. More recently, work reported from many sources by Sinet in Paris, and the discussion I have benefited from with Professeur Lejeune concerning superoxide dismutase levels and those of glutathione peroxidase in Down's Syndrome, has convinced me that my work with Vitamins may prove to have been as important to our children as anything else that I have done. It may be mentioned, though a single case does not constitute solid evidence, that a recent biochemical assay of my own daughter's blood surprised Sinet in that levels of superoxide dismutases were within normal limits in her case, though she is a classic trisomic and not a mosaic. Glutathione peroxidase, normally low in Down's Syndrome, was found to be *above* the norm for ordinary children.

To summarise the results of the work in such a short paper is difficult, but I must observe that a large proportion of the treated children fall now within the range of I.Q. (50-70) which allows them to attend schools for the Mildly Educationally Subnormal together with many otherwise normal but backward children instead of the schools for the Severely Subnormal to which they were almost invariably assigned in the past. The company of normal children is of crucial importance to Down's children, owing to their gift of social mimicry noted already by Down in 1866, when he first defined the condition. If placed in the unstimulating company of more severely affected children, who often have little or no speech, Down's children tend to decline, in my experience. If placed with slow but normal children, they steadily acquire more and more normal behaviour. The most advanced of the children whom we have treated (or rather whom their parents have treated with my guidance) have proved capable, in roughly thirty cases up to now, of profiting from education in normal schools at least up to the age of 11 so far, while two have entered normal secondary education. Most of our children are trisomic, and though our few mosaics tend to fall into the higher groups for intelligence, there are a number of equally able trisomics.

An average rise of intelligence was found of from 10 to 16 points above the I.Q.'s of control children reported in the literature, as in Smith and Berg (1976) as ranging from 41 to 45 on average. (Connolly (1978) gives means for males of 41.7 and for females 49.9). My own figures for

treated children are 54.88 for a sample of 32 boys aged between 4 and 16 years, and 60.25 for a sample of 27 girls. For my own "control" cases (which are not "pure" controls, but children whom I have treated from a variety of ages later than the end of the first year of life) the figures are respectively 44.699 for a sample of 30 boys aged 4 to 16, and 53.45 for a sample of 33 girls.

While these figures may not be dramatic, the effects of such a rise in mean intelligence are very great, for it makes all the difference in school placement of children into schools for the Mildly Subnormal (or in 1% of cases, into normal schools) instead of their formerly universal placement in schools for the Severely Subnormal. Their entire education is different, and their prospects of independent life after school days are greatly improved.

A further point which should be mentioned is that with certain precautions against the poor thermoregulation of Down's children, especially in infancy, when their autonomic response to cold conditions are abnormal, with a failure of vasoconstriction, and equal care in hot conditions when they cannot discharge waste heat enough owing to sharply diminished secretion of perspiration from the body (except for the head and neck which sweat profusely even in infancy) (Davidenkova (1966) and personal observations), we have been able to avoid serious illness in the majority of our children and have lost only 45 girls and 43 boys to date over a 14½ year period out of a total of around 3,000, a loss over that period of only around 3%, or, over the period of life from birth to 4 years where all our mortality has taken place, around 6½. This is a vastly improved figure from the 87% loss by the age 6 observed before World War II, and that of 60% by the age of 5 cited by some workers or even that of 50% cited by Record and Smith by the age of 1 year (1960).

Finally, may I cite a pertinent comment on child development by Penfield (1965). "The human brain is not a previously programmed calculator. It is a living growing changing organ. It can even carry out its own repairs to some extent. But it is subject to the inexorable evolution of its functional aptitudes. No one can alter the time-schedule of the human brain, not even a psychiatrist nor an educator. The built-in biological clock tells the passage of learning aptitudes and the teacher's opportunity". I propose, therefore, with much supporting evidence, that in the Down's Syndrome child at least, and in all probability in the normal child according to other studies, the first year of life is particularly crucial. If an intensive

programme of stimulation and dietary control is instituted early, I suggest that the whole picture of the Down's child as he has been in the past can be appreciably altered.

I have not had space here to acknowledge adequately the work of other workers. Indeed, I thought, until around 1969, that I was alone in the field, but have since found that such workers as the late Dr. Lydia de Coriat in Buenos Aires, Professor Rett in Vienna, Schmid in Germany, as well as Ludlow in England, Hanson in Oregon and a team of workers in Seattle, and Cunningham and Sloper (78) in Manchester, have quite independently of one another developed closely similar methods, with similar reported results, while my own figures have been frequently confirmed by independent educational psychologists when the children are tested at school age. To answer Clarke's criticism mentioned earlier that the experimenter and the assessor were in my case the same person, we have had since 1970 two separate testers, my colleague Mrs. Madge Morris of the Birmingham Schools Psychological Service and myself. Unlike myself, Mrs. Morris has no Down's child, or in fact any children of her own, and any bias which might be suggested in my own case would not be present in her. There is, however, very good inter-tester agreement. I must acknowledge here her ten years of most devoted work as she has given up practically every Saturday to the testing of Down's children, and with her husband was immensely helpful in tahulating with me recently the enormous mass of data from some 500 tests, from which the appended statistics have been calculated.

As Schmid (1969) wrote: "Es ist unverantwortlich, ein mongoloides Kind nicht zu behandeln". In concurring fully with this remark, I would add that of a far greater worker than either of us, with reference to a handicapped person, in the Gospel according to St. John, Chapter 9. "We must do the work of Him that sent me while it is still day, for the night is coming when no man can work". In no case does that apply more than in the case of the Down's Syndrome child.

EARLY TREATMENT AND TRAINING FOR THE CHILD WITH DOWN'S SYNDROME

R. BRINKWORTH AND M. MORRIS
Down's Children's Association - Birmingham, England - September 1980

PRELIMINARY ANALYSIS OF RESULTS: 1965-1980

Notes: The Control Groups quoted are defined as those children who have received treatment and training only subsequent to the end of their first year of life. Only those cited in the test, and those older children specified as Untreated (group 17b) were "pure" controls.

SUMMARY OF RESULTS (AUGUST 1980)

Chron. Age. (weeks)	Locomotor.	Personal/Social.	Hearing/Speech.	Eye/Hand.	Performance.	Practical R.	D.Q.	Skull. C.
GROUP 1. *Boys Age Range 16 to 25 weeks.* N = 9								N = 4
X = 19.33	X 90.98	X 100.8	X 85.5	X 92.9	X 95.2	...	X 96.75	X 40
SD = 3.32	SD 10.24	SD 12.78	SD 14.77	SD 10.4	SD 11.7	...	SD 12.77	SD 1.22
Girls Age Range 10 to 26 weeks. N = 8								N = 4
X = 20.625	X 88.68	X 96.15	X 84.85	X 92.03	X 93.44	...	X 89.49	X 39.75
SD = 5.90	SD 14.15	SD 14.26	SD 12.10	SD 19.49	SD 17.24	...	SD 11.21	SD 1.848
Controls (both sexes) See Text.								
GROUP 2. *Boys Age Range 26.6 to 38.5 weeks.* N = 16								N = 12
X = 31.8	X 82.2	X 89.94	X 78.68	X 92.27	X 89.67	...	X 86.22	X 42.98
SD = 4.65	SD 18.16	SD 18.24	SD 15.82	SD 15.21	SD 13.19	...	SD 14.23	SD 1.41
Girls Age Range 27.7 to 39 weeks. N = 15								N = 10
X = 32.39	X 81.73	X 87.45	X 78.16	X 92.18	X 85.25	...	X 84.97	X 41.4
SD = 3.79	SD 10.48	SD 14.02	SD 15.67	SD 14.20	SD 14.87	...	SD 11.18	SD 1.39
Controls N = 1								
33.4	64.8	79.8	54.8	79.8	79.8	...	71.8	...
Control Boys Age Range 30 to 38.3 weeks. N = 4								
X 31.8	X 41.1	X 53.01	X 47.29	X 41.56	X 45.73	...	X 50.03	...
SD 4.65	SD 16.6	SD 9.67	SD 11.58	SD 2.32	SD 8.12	...	SD 9.07	...
GROUP 3. *Boys Age range 40.3 to 49 weeks.* N = 10								N = 2
X = 45.4	X 80.11	X 85.71	X 79.63	X 85.84	X 82.95	...	X 83.28	X 45
SD = 3.01	SD 14.81	SD 12.66	SD 16.88	SD 17.62	SD 13.95	...	SD 13.72	...
Girls Age range 40 to 49.3 weeks. N = 14								N = 3
X = 44.2	X 79.90	X 92.0	X 82.99	X 92.75	X 87.63	...	X 86.93	X 42.6
SD = 2.98	SD 13.69	SD 14.03	SD 11.97	SD 12.19	SD 19.08	...	SD 11.31	...
Controls 1 only. Very good.								

Chron. Age. (weeks)	Locomotor.	Personal/Social.	Hearing/Speech.	Eye/Hand.	Performance.	Practical R.	D.Q.	Skull. C.
GROUP 4. *Boys Age range 50 to 59.3 weeks.* N = 14								N = 8
X = 55.26 SD = 2.99	X 74.33 SD 10.66	X 79.35 SD 9.01	X 75.89 SD 9.78	X 81.14 SD 9.88	X 79.83 SD 9.75	... ...	X 77.7 SD 7.43	X 44.62 SD 1.96
Girls Age range 51 to 59.8 weeks. N = 10								N = 7
X = 54.56 SD = 3.12	X 75.075 SD 12.20	X 87.93 SD 9.9	X 84.97 SD 6.817	X 84.06 SD 8.85	X 82.38 SD 7.05	... ...	X 82.55 SD 5.28	X 44.9 SD 1.64
Controls Boys Age range 50 to 57 weeks. N = 3								N = 1
X = 51.67 SD = 2.08	X 72.59 SD 6.49	X 73.6 SD 5.54	X 70.03 SD 11.57	X 79.6 SD 3.25	X 66.7 SD 2.87	... ...	X 72.7 SD 6.31	X 45.5 ...
Control Girls Age range 51.5 to 54.5 weeks. N = 2								N = 1
X = 53 SD = 2.12	X 64.55 SD 18.45	X 59.8 SD 11.45	X 56.9 SD 21.07	X 69.55 SD 11.38	X 59.7 SD 11.59	... ...	X 60.2 SD 17.25	X 42.25 ...
GROUP 5. *Boys Age range 58 to 68 weeks.* N = 17								N = 6
X = 63.8 SD = 3.05	X 71.28 SD 10.66	X 79.13 SD 13.72	X 75.40 SD 11.33	X 83.74 SD 13.99	X 75.49 SD 10.18	... ...	X 77.17 SD 9.696	X 46.58 SD 0.92
Girls Age range 60 to 66 weeks. N = 5								N = 3
X = 63.8 SD = 2.39	X 72.1 SD 9.98	X 86.43 SD 11.66	X 75.83 SD 12.7	X 80.72 SD 7.26	X 73.39 SD 4.88	... ...	X 77.63 SD 8.31	X 44.8 SD 0.76
Control Boys Age range 66 to 69 weeks. N = 4								N = 3
X = 68 SD = 1.41	X 51.25 SD 14.54	X 61.77 SD 7.43	X 63.7 SD 9.45	X 69.4 SD 8.92	X 66.77 SD 12.88	... ...	X 60.24 SD 11.51	X 45.67 SD 1.15
Control Girls Age range 60 to 66 weeks. N = 2								N = 1
X = 63 SD = 4.24	X 56.9 SD 9.05	X 84.96 SD 6.55	X 83.99 SD 0.94	X 82.4 SD 5.94	X 67.84 SD 0.48	... ...	X 75.5 SD 2.12	X 45 ...
GROUP 6. *Boys Age range 70 to 77 weeks.* N = 4								N = 4
X = 74 SD = 3.16	X 70.025 SD 13.25	X 69.5 SD 8.54	X 63.86 SD 6.18	X 67.19 SD 7.26	X 61.8 SD 7.86	... ...	X 63.52 SD 3.84	X 45.25 SD 0.5
Girls Age range 70 to 79 weeks. N = 7								N = 3
X = 75.57 SD = 3.16	X 55.66 SD 13.26	X 69.85 SD 8.54	X 65.93 SD 6.18	X 75.97 SD 7.26	X 70.52 SD 7.86	... ...	X 70.25 SD 3.84	X 44.166 SD 0.763

Control Boys only Age range 72 to 76 weeks. N = 4								N = 4
X = 74	X 56.26	X 62.56	X 64.04	X 55.65	X 59.45	...	X 64.25	X 46.625
SD = 1.82	SD 9.35	SD 15.99	SD 14.83	SD 13.08	SD 9.38	...	SD 1.89	SD 2.29
GROUP 7. *Boys Age range 81 to 88 weeks.* N = 12								N = 6
X = 83.75	X 66.69	X 78.94	X 71.32	X 75.52	X 68.37	...	X 72.19	X 45.75
SD = 2.93	SD 12.76	SD 8.78	SD 11.54	SD 10.17	SD 12.92	...	SD 8.67	SD 1.08
Girls Age range 82 to 88 weeks. N = 9								N = 2
X = 85.5	X 71.6	X 78.74	X 68.37	X 76.5	X 67.57	...	X 72.44	X 46
SD = 2.01	SD 15.07	SD 9.34	SD 9.69	SD 10.29	SD 11.37	...	SD 9.96	...
Control Boys Age range 86 to 88 weeks. N = 2								N = 1
X = 87	X 49.78	X 71.4	X 59.75	X 74.5	X 67.81	...	X 64.5	X 45.5
SD = 1.41	SD 7.38	SD 5.09	SD 3.18	SD 7.78	SD 13.70	...	SD 6.36	...
Control Girls Age range 85 weeks only. N = 2								N = 1
X = 85	X 44.05	X 56.8	X 53.35	X 68.5	X 45.5	...	X 53.5	X 47
SD = 0	SD 6.86	SD 13.85	SD 20.01	SD 6.36	SD 11.74	...	SD 12.02	...
GROUP 8. *Boys Age range 90 to 103.3 weeks.* N = 20								N = 4
X = 95.60	X 61.24	X 69.91	X 60.83	X 71.22	X 60.93	...	X 64.88	X 46
SD = 4.38	SD 14.20	SD 9.57	SD 11.7	SD 9.46	SD 12.38	...	SD 8.64	SD 1.78
Girls Age range 90 to 101.6 weeks. N = 10								N = 3
X = 95.06	X 62.12	X 74.75	X 67.59	X 72.17	X 70.90	...	X 69.88	X 44.93
SD = 3.75	SD 11.88	SD 12.38	SD 10.09	SD 5.73	SD 9.835	...	SD 7.55	SD 0.60
Control Boys Age range 89.5 to 102.5 weeks. N = 6								N = 3
X = 94.9	X 60.37	X 62.5	X 56.19	X 66.75	X 62.44	...	X 61.8	X 44.7
SD = 4.72	SD 11.08	SD 9.81	SD 17.87	SD 13.81	SD 17.90	...	SD 10.71	SD 1.96
Control Girls Age range 90.5 to 98 weeks. N = 2								N = 1
X = 94.25	X 80.85	X 66.17	X 60.70	X 71.30	X 75.7	...	X 70.7	X 47
SD = 5.30	SD 12.88	SD 2.84	SD 3.71	SD 0.5	SD 11.94	...	SD 5.23	...
GROUP 9. *Boys Age range 2 — 3 years* (two groups). N = 23								N = 11
X 29.44	X 62.73	X 67.19	X 55.56	X 66.02	X 66.7	...	X 63.2	X 47.23
SD 3.13	SD 15.96	SD 9.96	SD 10.93	SD 9.21	SD 12.51	...	SD 10.30	SD 1.10

Chron. Age. (weeks)	Locomotor.	Personal/Social.	Hearing/Speech.	Eye/Hand.	Performance.	Practical R.	D.Q.	Skull. C.
	Girls Age range 2 — 3 years. N = 24							N = 9
X 31.85	X 65.58	X 71.08	X 64.03	X 67.49	X 63.91	...	X 66.33	X 45.8
SD 3.87	SD 13.59	SD 11.45	SD 12.41	SD 9.66	SD 11.84	...	SD 9.545	SD 1.08
	Control Boys Age range 2 — 3 years. N = 11							N = 7
X 28.84	X 64.02	X 63.69	X 50.75	X 58.69	X 51.44	...	X 57.39	X 47.14
SD 5.52	SD 18.46	SD 17.24	SD 19.14	SD 16.26	SD 18.12	...	SD 15.92	SD 1.435
	Control Girls Age range 2 — 3 years. N = 6							N = 2
X 28.83	X 57.98	X 70.73	X 57.9	X 65.98	X 68.02	...	X 64.27	X 46
SD 4.71	SD 14.82	SD 6.27	SD 7.78	SD 2.32	SD 10.95	...	SD 6.24	...
GROUP 10. *Boys Age range 40 to 47 months.* N = 8								N = 5
X 43.37	X 58.18	X 61.1	X 51.93	X 52.04	X 54.42	X 55.22	X 53.86	X 48.2
SD 2.76	SD 16.52	SD 18.98	SD 18.38	SD 11.22	SD 11.65	SD 5.31	SD 12.11	SD 1.79
	Girls Age range 38 to 47 months. N = 14							N = 4
X 42.5	X 55.18	X 70.53	X 53.43	X 64.02	X 66.07	X 62.64	X 61.41	X 47.5
SD 2.83	SD 11.30	SD 14.71	SD 18.28	SD 8.73	SD 15.21	SD 11.00	SD 10.95	SD 1.91
	Control Boys Age range 36½ months to 47 months. N = 15							N = 5
X 42.87	X 51.23	X 55.75	X 41.4	X 53.45	X 50.87	X 57.7	X 50.22	X 47.1
SD 3.49	SD 7.74	SD 10.76	SD 13.23	SD 10.52	SD 12.96	SD 13.63	SD 8.31	SD 1.63
	Control Girls Age range 37 to 47 months.							N = 5
X 42.20	X 55.88	X 54.08	X 52.18	X 53.03	X 51.25	X 56.05	X 52.88	X 47.4
SD 4.36	SD 5.51	SD 8.29	SD 9.44	SD 10.03	SD 17.72	SD 1.06	SD 8.87	SD 1.14
GROUP 11. *Boys Age range 51 to 59 months.* N = 12								N = 4
X 53.33	X 56.5	X 59.72	X 44.54	X 59.6	X 50.1	...	X 52	X 48.75
SD 5.87	SD 15.85	SD 17.31	SD 9.72	SD 11.37	SD 15.24	...	SD 8.82	SD 1.70
	Girls Age range 46 to 58 months. N = 6							N = 4
X 53.17	X 61.08	X 62.77	X 50.27	X 55.21	X 55.48	...	X 56	X 47.37
SD 5.11	SD 13.69	SD 8.86	SD 16.92	SD 12.25	SD 12.16	...	SD 10.29	SD 1.70
	Control Boys Age range 44 to 55 months. N = 5							N = 3
X 52.6	X 58.72	X 57.3	X 41.92	X 55.8	X 53.28	...	X 51.82	X 48.5
SD 5.50	SD 22.39	SD 6.87	SD 4.90	SD 10.79	SD 9.07	...	SD 7.37	SD 1.32

Control Girls Age range 49 to 55 months. N = 11								N = 8
X 50.54	X 55.59	X 58.73	X 51.89	X 53.12	X 50.7	...	X 55.09	X 47.8
SD 3.98	SD 10.59	SD 16.98	SD 15.59	SD 10.11	SD 14.56	...	SD 13.19	SD 1.89
GROUP 12. *Boys Age range 59 to 64 months.* N = 6								N = 2
X 60.08	X 59.68	X 59.72	X 48.6	X 51.53	X 51.87	...	X 53.33	X 50.25
SD 1.83	SD 15.03	SD 12.35	SD 9.02	SD 13.03	SD 15.60	...	SD 11.15	SD .35
Girls Age range 60 to 71 months. N = 7								N = 2
X 65.57	X 55.46	X 72.36	X 55.16	X 59.83	X 59.81	...	X 60.28	X 46.5
SD 3.69	SD 13.15	SD 10.14	SD 11.99	SD 12.89	SD 18.0	...	SD 10.67	SD 2.12
Control Boys Age range 61 to 70 months. N = 6								N = 3
X 64.83	X 49.28	X 52.3	X 31.5	X 42.93	X 46.07	...	X 44.17	X 48.83
SD 3.06	SD 12.26	SD 12.85	SD 6.76	SD 7.46	SD 10.63	...	SD 8.70	SD .76
Control Girls Age range 60 to 70 months. N = 2								N = 3
X 67.00	X 55.8	X 64.27	X 52.08	X 53.92	X 56.28	...	X 55.8	X 49.00
SD 3.90	SD 11.82	SD 12.04	SD 18.63	SD 5.47	SD 10.86	...	SD 8.42	SD 2.60
GROUP 13. *Boys Age range 75 to 79 months.* N = 3								N = 3
X 77.67	X 52.4	X 52.23	X 38.35	X 48.77	X 37.27	X 55.5	X 46.76	X 50.0
SD 2.31	SD 26.30	SD 27.48	SD 21.89	SD 35.50	SD 20.88	SD 14.49	SD 25.71	SD 1.0
Girls Age range 72 to 83 months. N = 7								N = 2
X 77.78	X 68.21	X 81.63	X 58.66	X 65.86	X 66.2	X 60.21	X 67.38	X 48.25
SD 3.63	SD 12.67	SD 8.74	SD 12.15	SD 8.50	SD 5.15	SD 10.87	SD 6.78	SD 2.47
Control Boys Age range 72 to 81 months. N = 4								N = 2
X 75.75	X 57.32	X 50.12	X 40.22	X 41.07	X 42.77	X 39.94	X 45.32	X 50.0
SD 3.86	SD 11.98	SD 13.17	SD 7.38	SD 2.77	SD 10.61	SD 11.44	SD 8.45	...
Control Girls. 1 only								
80.5 months	57.0	62.1	67.0	62.6	49.6	69.56	61.2	...
GROUP 14. *Boys Age range 84 to 95 months.* N = 6								N = 4
X 90.0	X 62.76	X 73.03	X 61.48	X 64.93	X 57.70	...	X 62.0	X 48.0
SD 4.29	SD 9.38	SD 11.34	SD 10.79	SD 9.38	SD 21.07	...	SD 6.70	SD 1.0
Girls Age range 88 to 90 months. N = 3								
X 89.0	X 57.67	X 69.9	X 52.33	X 53.03	X 62.47	...	X 57.67	...
SD 1.0	SD 21.70	SD 3.26	SD 1.72	SD 4.80	SD 2.28	...	SD 2.52	...

Chron. Age. (weeks)	Locomotor.	Personal/Social.	Hearing/Speech.	Eye/Hand.	Performance.	Practical R.	D.Q.	Skull. C.
	Control Boys Age range 84 to 89 months. N = 5							N = 3
X 86.4	X 56.2	X 53.1	X 31.28	X 40.14	X 44.38	...	X 43.6	X 50.0
SD 2.51	SD 17.35	SD 18.31	SD 9.25	SD 14.78	SD 11.47	...	SD 11.61	SD 1.0
	Control Girls Age range 92 to 93 months. N = 2							
X 92.5	X 56.9	X 55.5	X 47.15	X 52.85	X 42.35	...	X 51.0	X 50.0
SD 0.71	SD 48.65	SD 53.5	SD 37.83	SD 48.15	SD 38.53	...	SD 45.25	...
GROUP 15. *Boys Age range 97 to 104 months.* N = 3								N = 1
X 100.0	X 59.83	X 73.27	X 51.27	X 57.13	X 54.5	...	X 57.0	X 49.0
SD 3.60	SD 5.58	SD 6.80	SD 11.30	SD 11.19	SD 13.97	...	SD 9.54	...
	Girls Age 101 months. 1 only							
X 101.0	X 69.3	X 85.1	X 65.3	X 67.3	X 83.1	...	X 73.0	...
	Control Boys Age range 99 to 102 months. N = 2							N = 1
X 100.5	X 39.25	X 43.5	X 32.3	X 31.8	X 37.1	...	X 41.5	X 50.0
SD 2.12	SD 12.66	SD 12.3	SD 2.54	SD 6.08	SD 21.35	...	SD 21.35	...
	Control Girls Age range 100 to 101 months. N = 3							N = 1
X 100.67	X 52.9	X 65.43	X 51.27	X 57.17	X 53.5	...	X 54.67	X 48.0
SD 0.58	SD 19.05	SD 25.97	SD 26.23	SD 26.34	SD 29.43	...	SD 25.73	...
GROUP 16. *Boys 1 Case. Age range 9 to 10 years*								
109 months	X 60.5	X 64.2	X 42.2	X 57.3	X 53.0	X 55.0	X 55.0	...
	Girls None							
	Control Boys Age range 110 to 116 months. N = 3							N = 1
X 113.0	X 51.0	X 52.93	X 46.27	X 43.97	X 44.6	X 42.43	X 46.96	X 51.0
SD 3.0	SD 9.46	SD 19.51	SD 14.11	SD 14.00	SD 14.28	SD 18.41	SD 14.43	...
	Control Girls Age range 105 to 116 months. N = 3							N = 1
X 111.78	X 52.13	X 52.63	X 39.0	X 42.3	X 45.2	X 41.5	X 45.23	X 50.0
SD 5.42	SD 15.39	SD 21.45	SD 13.01	SD 17.13	SD 19.51	SD 13.88	SD 16.41	...

Chron. Age. (weeks)	Locomotor.	Personal/Social.	Hearing/Speech.	Eye/Hand.	Performance.	Practical R.	D.Q.	Skull. C.
GROUP 17. *Girls only. Age range 130 to 131 months.* N = 2 (Age range 10 to 11 years)								
X 130.5	X 60.45	X 61.25	X 45.95	X 58.15	X 45.95	...	X 54.0	...
SD 0.71	SD 2.9	SD 1.77	SD 8.98	SD 6.15	SD 1.91	...	SD 1.41	...
Untreated Control Boys Age range 121 to 125 months. N = 4								N = 4
X 124.0	X 36.67	X 37.05	X 20.06	X 37.52	X 51.27	...	X 35.60	X 51.0
SD 2.16	SD 6.19	SD 9.90	SD 8.04	SD 14.43	SD 17.94	...	SD 5.94	SD 0.82
Partially Treated Control Girls Age range 120 to 122 months. N = 2								N = 2
X 121.0	X 76.85	X 59.45	X 58.6	X 73.5	X 54.4	...	X 63.5	X 49.75
SD 1.41	SD 4.45	SD 1.63	SD 2.83	SD 4.95	SD 11.03	...	SD 2.12	SD 0.35

All Age Samples. Ages 4 to 16 years. Developmental Quotient only.

Experimental Boys. N = 32	*Experimental Girls. N = 27*	*Controls (treated from later than 1 year of age)*	
		Boys N = 30	*Girls N = 33*
X 54.88	X 60.25	X 44.699	X 53.45
SD 11.48	SD 9.86	SD 10.13	SD 14.94

Addendum. It should be noted that results for the experimental and Control I cases are not fully representative of the *highest* levels reached, as there has been a natural tendency for parents of children with certain problems to refer them for assessment. Contrariwise, those children who are succeeding best, and are attending ordinary schoools, are not referred, though independent reports from their own Educational psychologists give I.Q's between 70 and 101. It is planned to call in the more advanced cases in the 1980-81 session, and averages may well then need to be revised to a higher level, possibly in both categories.

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TWO EXPERIMENTS IN SOCIAL REHABILITATION

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After these highly scientific presentations, my contribution will be of a completely different nature. With your permission I shall speak of my own experience.

When I studied to become a teacher for the handicapped, my basic idea was that with these children who were mentally handicapped, it was necessary to use whatever possibilities they still had, to help them to become as nearly self-sufficient in their daily life, teach them if possible to read, to write—in short, help them to become as nearly as possible like the child whose intelligence is intact. Then I learned about an experiment which, while it followed this idea that we must help the child to progress, gave me another view of him as a person.

THE EXPERIMENT OF *l'Arche* (THE ARCH)

I had occasion to become acquainted with a project called *l'Arche,* created by Jean Vanier. Jean Vanier, whom you may perhaps know, was a doctor of philosophy. He was teaching in Toronto when he met some seriously mentally handicapped persons. He was teaching them painting. Jean Vanier was struck by the difference in the way the normal students regarded him and the way the mentally handicapped pupils regarded him. His regular students saw him only in terms of their own future. He was of interest to them to the extent that he could help them to pass their examinations as well as possible. But aside from this his inner self did not interest them. Not one of them cared at all about what would happen to Jean Vanier the next year. On the other hand, it seemed to him in his contacts with the handicapped students that they were interested in him as a person: "Jean", that they were worried if he was tired or if he had

some problems, they were anxious to know when he would return; these people, who were handicapped in their intelligence were not at all handicapped in their hearts, their feelings, or in their capacity to relate to others. Quite the contrary: to the degree to which they seemed handicapped in their intelligence, their ability to feel affection and relate to others seemed more developed than that of other people.

And that is how Jean Vanier decided to abandon teaching philosophy and to spend his life with three seriously handicapped persons whom he had come to know on his visits to psychiatric hospitals. His intention at the time was to limit himself to these three persons. (He had a car that could hold four people, and he wanted to be able to go out with them on Sundays). He shared his daily life and needs with them: cooking together, working together, relaxing, receiving visits of friends.

When I went for the first time to visit *l'Arche,* I had already visited many institutions in France and in other countries. I was very much impressed by the difference in the atmosphere between these specialized centers and the atmosphere of the little house of *l'Arche,* where, fourteen years ago, I was invited to spend an evening. At that time the little *Arche* had already grown. There were twelve persons: six assistants, young people, and six mentally handicapped persons. I was at once deeply impressed hy the air of simplicity, of truth, of spiritual hunger. Jean Vanier told me that what actually had attracted him to these persons who had been treated as outcasts was their capacity for love and their appeal for affection from their surroundings.

Subsequently I had many examples (and you too must have had if you have contact with mentally handicapped persons) of the strength of their affection. When I arrive at *l'Arche,* or when a new visitor arrives at *l'Arche,* no one is interested to know if he has a small car or a big Rolls Royce, whether he has a fur coat or a patched vest. You are immediately separated from your status, your titles or your degrees and your decorations. You are a person: Marie-Hélène, John or Pierre. And handicapped persons, perhaps more than all others, because they do not reason, have an intuition about the person with whom they are talking. They seem to be able to tell whether that person likes them or not. That is why it is so important to create around them a small community where each one of them is in company and is recognized, where all their potential emotional values, their affections, their social qualities and ability to relate to others, can develop.

To continue the story of *l'Arche,* I want to say that this very small initiative attracted the interest of a certain number of persons from various

countries, who were struck by the expansiveness of the handicapped persons living there and by their progress. Some of them who had come from psychiatric hospitals had arrived very anguished, very aggressive. After several months (sometimes after several years), feeling that they were welcome just as they were, with their problems, their disturbances, they seemed to find gradually a deep peace of heart and became capable of being themselves elements of peace and helpers in the community.

Some young persons and some less young came to *l'Arche* for a time, then they returned to their home town to establish there similar communities of 10, 12, 16 persons, living in village houses, or in an apartment.

In these communities you do not find the handicapped on one side and the instructors on the other side. There is a family, whose members all live the same life together. The teachers do not receive pay, just as the mother and father of a family are not paid. This requires from those who come there, whether it be for a long or a short period, a great availability. I am always impressed to see that there are young people who are willing to undertake such work, for this involves their whole being. And they all say: "We have received much more than we have given, for we have rediscovered the basic human values, that is, the sincerity of relations between people, simplicity, not the desire to make money, to achieve success and fame".

There now exist *Arches* in a dozen countries, as different as Denmark, Norway, Haiti, the Ivory Coast, Upper Volta, the United States, Canada, India, France, Belgium. *L'Arche* tries to integrate itself with the culture and way of life of each country, and so the *Arches* differ widely from one country to another. In Honduras they live very poorly; in Denmark, where the living standard is high, the *Arche* members live in a way which by and large corresponds to the living standard of Copenhagen. But everywhere there is this same atmospbere where each person is received just as he is, for what he is, with his own values, capable of creating a certain atmosphere of peace, unity and faith around him.

I believe that *l'Arche* has much to teach us about the values of the handicapped person. Yesterday we spoke of the conflicts throughout the world, of the terrible problems which exist in some countries on the most elementary level: that of food, and the lack of solidarity among different countries. I believe that instead the bandicapped person, if he is really accepted just as he is, in small communities, can be an instrument for peace and harmony in our world so profoundly disturbed. In the tragedy of tbe birth of a handicapped child in a family, I am always very much surprised to see how similar are the reactions of the parents.

Whether one is a watchman in a factory or a Doctor of Philosophy, the suffering, the bewilderment are always the same. And that is how this trial brings close together those who are touched hy this tragedy.

THE EXPERIMENT OF *Foi et Lumière* (FAITH AND LIGHT)

I would like now to say a word about another experiment which started out in a small way and which was born from the isolation and the appeal of one family. This initiative can spread much more easily than *l'Arche* because it does not require financial means, or administrative formalities, or life engagement. (In effect, *l'Arche* requires the presence of assistants who commit themselves to sharing their daily life with the handicapped persons, a thing which is not so easily found. Most teachers want to work six hours a day, and then they return home and live like everyone else). This other experiment was called "Faith and Light". It is very modest in a certain sense, but it is also very significant. It was born from the distress of a family whose only two children were seriously mentally handicapped. This family had decided to go to Lourdes, a place of pilgrimage for the sick and handicapped. That was twelve years ago! When the parents wanted to enlist in their parish pilgrimage, they were told, "That is not possible, we cannot accept mentally handicapped persons, that would cause trouble, and in Lourdes it might interfere with the ceremonies and the various religious rites. And then, what good would such an experience do to your children, whose intelligence is like that of an 18-month old child?".

So these parents decided to go on a pilgrimage without being part of any organization. In Lourdes, the city of the sick and handicapped, the city of suffering, they felt complete rejection from most of the people they met, at the hotel, in the street or at the grotto. They heard comments such as: «When one has children as handicapped as those, they should leave them at home", or "It is too disturbing to our sensitivities, those children should not be seen".

This was in 1968. The mother of these two children told Jean Vanier and me how she and her husband had been hurt by their visit to Lourdes. All four of them had found themselves more completely isolated than they had ever felt at home on their farm in the country.

And just then we had an inspiration. Why don't we try to organize a pilgrimage especially for mentally handicapped persons of all ages and their families? So that they would not find themselves once more left to themselves, in ghettos, we thought of inviting some young people

and their friends. And finally, so that this pilgrimage should not prove to be a "feu de paille" (a flash in the pan), we would prepare them in small groups of about thirty people—parents, friends, and the handicapped. We discussed this idea among us. Each time there was some response of agreement and so we progressed slowly toward the realization of this project. Small groups were formed, they met every month for periods of reflection, of prayer, of organization and of entertainment. Three years later, in 1971, we met in Lourdes, 12,000 persons from 15 countries. Four thousand among us were mentally handicapped.

During the preparation we were able to foresee what might be the fears of a whole city. The city of Lourdes, when it learned of our project, went into what we might call a panic. They all wondered what would happen. We held several meetings at several levels to undramatize and prepare the people. It was a question of Lourdes adapting to these new pilgrims, of providing ceremonies that would be very simple and at the same time very impressive, of furnishing all security measures at all levels.

Lourdes, before our arrival, was a little prepared for war: the river was lined with a soldier every 50 meters to prevent children and adults from falling or throwing themselves into the river. The outside roads were guarded by police in case anyone tried to run away. And, on the eve of the day we arrived, some of the trades people had lowered their metal shutters fearing that their stores might be sacked. Then we arrived. And for three days it was a great surprise, a great revelation. Everyone saw this crowd of people full of joy and peace who sang "Alleluia" from morning to evening, for it was the only word they all knew in common. In all languages and at all intellectual levels, it was "Alleluia". "Alleluia" to say good morning, to say good night, to say thank you, to say pardon me. Never had Lourdes seen such an explosion of joy. This is explained, I believe, by the fact that the handicapped people who were there felt deep in their hearts that all this was being done because of them and for them, and that it was they who were bringing joy to the others.

There were no spectacular miracles, or brains healed, but there were truly "little miracles". A child who smiled for the first time at the grotto, another who in the middle of the feast (for we did have a big feast) began to smile and to clap his hands like everyone else. For the parents too this was a sort of miracle to see young people become interested in their child and to see that their child could bring joy to others. Many said, "At Lourdes we have seen our child in a completely new light". In

brief, an experiment in the communication of mutual happiness, which caused this great explosion of joy on Easter in 1971.

Since then Lourdes has opened its arms more and more to mentally handicapped persons. It is becoming increasingly customary for diocesan pilgrimages to welcome families with a handicapped child among their pilgrims. We are now preparing another pilgrimage for Easter 1981 on the tenth anniversary of the first pilgrimage. We had a meeting last week regarding this with all the authorities of Lourdes. But this time the meeting took place peacefully and serenely, even if the precautions finally decided upon were the same as those of 1971. Everyone had pleasant memories of ten years ago.

Since that first pilgrimage, the small communities which were created have continued to meet regularly. One sees in these groups changes which are sometimes profound: parents who accept their child as he is; young people who are often discouraged or in revolt because of the lack of a true ideal, find a form of involvement which they would not find elsewhere.

Faith and Light now exists in 23 countries. It is, as I said earlier, something very simple. In order to create a community, there is no need for money or particular authorization, or large quarters. Meetings are held in one family or another. No need for cumbersome structures. A few young people, with their guitars, and then some families. They sing, they dance, they meditate, they also pray. But with so little the life of many families, of handicapped persons, has been changed. Simply because bridges have been built between them and society.

Testimony of one family

In closing I would like to quote one particular testimony. The person lives close by. It is a family of Rome whose child, who is now 18 years old, was born seriously handicapped. They were not immediately aware of this, but after a few weeks and then a few months they realized that Sabina was blind, then that she was deaf, and then that she was very seriously handicapped mentally. Moreover, she cried almost every night. Life for her parents was an inferno (I speak very frankly because they have declared their willingness to write their story). After learning of Sabina's handicap, they practically built a wall around themselves and their daughter. They made all kinds of excuses in order to avoid taking part in family celebrations, weddings, baptisms. Sabina's father began to work long hours so that he would come home as late as possible. On

Sunday he would go to the soccer game even though he was not at all interested in soccer, rather than to find himself condemned to be with his wife and daughter. This situation lasted several years. The family was completely broken up. Everyday relationships no longer existed, there was only indifference and aggressiveness. There they were, without any bonds between them and without any bonds with society.

One day (this sounds like a fairy tale, for which I hope you'll forgive me) the parents received a telephone call from a young man: «Could Sabina come to one of our meetings?" They feared it was some joke, in very bad taste. They replied, "Do you know who Sabina is? Sabina is a seriously handicapped person. She is not able to attend any meeting". The young people from *Foi et Lumière* (Faith and Light) who were telephoning insisted saying, "But of course, we have a meeting which she could very well attend, where she would find herself at home". Briefly, then, tired of arguing, the parents consented. They allowed the young people to come and call for Sabina, who was very happy to go with them and attended her first meeting of Faith and Light. She spent most of her time there shouting. But the young people were not discouraged. Despite all the disturbance which was involved, every month they would go and call for Sabina to take her to the meeting. Then one day the young people suggested that they take Sabina to a vacation camp with them. At that point the parents became very hostile. They said, "She is going to upset all the activities of your camp and she won't be able to get any benefit from that". Finally, again, they agreed. Sabina went to the camp. The young people took turns each night, in a separate tent, watching over Sabina who screamed all through the night. But they returned with a much more relaxed Sabina. She had made some contacts and especially had become friendly with some particular persons. From that moment on, Sabina's progress, though very slow, has continued. Her parents after a while also came themselves to the meetings of Faith and Light.

I saw Sabina last Sunday at one of these meetings. She goes from one to the other, she communicates, she recognizes her father. As she approaches him, she jumps up to embrace him. Her parents have taken a serious active part in the movement. To those parents who are desperate or rebellious, Francesco and Olga can say, "We too have been through all that, we understand".

I wanted to end with this example. It shows that without great financial means but simply by building bridges to the families, by creating contacts with their children, much can be changed in the lives of mentally

handicapped persons and their parents, for they will react according to their surroundings. If the attitude of their family changes, they too will change.

I believe—and we have heard it said several times during this meeting—that on the political level there is very little that we can change. But it seems to me that we can all do something to change the attitudes and sympathies with regard to the handicapped, so that they will come to be regarded not as persons who lack something, but as people who can contribute something, whose life has a deep meaning. With hope we can change, certainly not all of society, but at least the life of some families who are carrying a very heavy burden and who therefore are very poor. That I believe is the real meaning of these two experiments of *l'Arche* and of *Faith and Light* which I have described to you.

CONCLUSIONS

Mental deficiency is a condition peculiar to man for it prevents the individual from fully participating in his human heritage. To assess precisely the general incidence of mental deficiency is a difficult task, but its importance can be measured by the following figures. Including all disabilities, roughly 10% of the world population is affected by a physical, sensory or mental affliction. Nearly 3% of the world population, in a conservative estimate, i.e. more than a hundred million persons, are suffering from permanent mental ailment reducing their intelligence to an extent not compatible with independent ordinary everyday life. Hence among the other scourges of humanity like malnutrition, extreme poverty and deprivation, mental deficiency is the most important obstacle to fulfillment of human potential.

Causes

Mental deficiency is a symptom of diseases which can affect a person at any age or stage of life.

At conception genetic errors, mutations or chromosomal aberrations, are probably the most important factors. Very early in fetal life infection such as rubella or toxoplasmosis, toxic agents such as drugs, alcohol and methyl mercury and exogenous factors such as radiations are the greatest danger.

Later, complications of pregnancy, delivery and the early neonatal period may damage the brain of the previously healthy baby and these problems may be aggravated by inadequate care of mother and child. Failure of parental and especially maternal attachment to the child may add deprivation to disability and rejection of breast feeding can cause childhood malnutrition to exert earlier its sinister effects. During childhood, infections and trauma may play a great role and later in life a wide array of accidents and diseases can also profoundly reduce mental efficiency.

From an etiological viewpoint one could classify severe mental deficiency into four categories, with the approximate frequencies: genetic diseases (30%), chromosomal abnormalities (20%), exogenous causes including adverse effects in utero and early life (30%). The remaining causes (20%) are still not identified. Mental deficiency from any of these causes may be aggravated by social deprivation and malnutrition.

As a general impression we are not aware that a diminution of these causes is foreseeable. Some of them may well be increasing in future years, especially those of environmental origin, both physical and social.

Health measures

a) *Prevention:* When relevant action is possible before definitive lesions are produced, prevention is the best protection. Many examples are available: vaccination of the future mother against infection—treatment of the fetus allowing for relief of haemolytic anaemia due to Rh incompatibility—improved care during pregnancy and labour—or, postnatally, special diets to prevent the dangerous effects of genetic factors such as phenylketonuria and galactosaemia—and generally any measures preventing brain injury are of great importance; this includes all surgical procedures as in craniostenosis and hydrocephaly.

In cases in which a high risk is predicted, counselling and advice for the families is necessary. General public information is also indispensable.

b) *Medical treatment:* When lesions are already established, medical treatment is generally limited but there are many reasons to believe that the situation will improve in many cases. Medication can stop the progress of the disease, can alleviate some of the symptoms and stimulate the compensatory functions of the brain.

c) *Dangers to the mentally deficient:* Although a number of chromosomal and genetic causes of mental deficiency can be diagnosed in the young fetus, at present no effective treatment can be offered. This lack of treatment has led to the proposal and to the use of termination of pregnancy or more accurately to the extermination of the fetus. This behaviour is very disturbing because it represents a policy which would be regarded as antihuman if applied to any other age group or disorder. Similarly, the deliberate neglect, the calculated starvation or even the poisoning of the handicapped newborn, recommended and practised by some doctors defies not only traditional medical ethics but the most elementary rules of human conduct: our duty of care and protection is greater, the weaker and more helpless the victim.

On the contrary we believe that early diagnosis will and must be pursued to increase the efficiency of therapy. For instance amniocentesis already quoted, could be used successfully against inborn diseases as it has been used in the case of haemolytic disease of the newborn.

As scientists we consider also that early detection by various means, such as fetoscopy, will greatly improve our ability to cure many others.